1. Name of the Medicinal Product

Mirena 52 mg Intrauterine Delivery System

2. Qualitative and Quantitative Composition

Active substance:

Levonorgestrel 52mg.

For the full list of excipients, see Section 6.1.

3. Pharmaceutical Form

Intrauterine delivery system.

The levonorgestrel intrauterine delivery system 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-frame of Mirena contains barium sulphate, which makes it visible in X-ray examination. The vertical stem of the intrauterine delivery system is loaded in the insertion tube at the tip of the inserter.

4. Clinical Particulars

4.1 Therapeutic Indications

Contraception.
Idiopathic menorrhagia.
Protection from endometrial hyperplasia during oestrogen replacement therapy.

4.2 Posology and Method of Administration

4.2.1 Method of administration

Mirena is inserted into the uterine cavity and is effective for 6 years in the indication contraception and 5 years in the indication idiopathic menorrhagia and protection from endometrial hyperplasia during oestrogen replacement therapy.

4.2.1.1 Contraception and idiopathic menorrhagia

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.

Post-partum insertion
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 immediately taken, such as physical examination and ultrasound. Physical examination alone (including checking of threads) may not be sufficient to exclude partial perforation.

4.2.1.2 Protection from endometrial hyperplasia during oestrogen replacement therapy

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

In women on hormone replacement therapy, Mirena can be used in combination with oral or transdermal oestrogen preparations without progestogens.

Mirena should be used with caution in postmenopausal women with advanced uterine atrophy. Controlled clinical trials were done in previously parous women aged mainly over 18 years. Use of this product before menarche is not indicated. (See Section 4.4).

4.2.1.3 Insertion and removal/replacement

It is strongly 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. Mirena must be inserted using aseptic technique.

Mirena is removed by gently pulling on the threads with a forceps. If the threads are not visible and the 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.

The system should be removed after 6 years in the indication contraception and after 5 years in the indication idiopathic menorrhagia and protection from endometrial hyperplasia during oestrogen replacement therapy. If the user wishes to continue using the same method, a new system can be inserted at the same time.

Removal of Mirena can occur at any time during the cycle. If ongoing contraception is desired, the timing of initiation of the method chosen will depend upon when in the cycle Mirena is removed.

If removal is to occur within the first 7 days of the onset of menstruation, a new Mirena, another levonorgestrel-intrauterine system (LNG-IUS) or other hormonal contraceptive can be initiated immediately.

If removal is to occur beyond the first 7 days of the onset of menstruation or the menses are irregular, the woman may be at risk of pregnancy if she has had intercourse in the past week. If the woman chooses another Mirena or LNG-IUS continuous contraception is provided. If other hormonal contraception is desired it should be started 7 days before the removal to ensure continuous contraception; otherwise, a barrier method of contraception should be used or the patient should abstain from vaginal intercourse for 7 days to prevent pregnancy.

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 intrauterine system (IUS) has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

Instructions for use and handling

Mirena is supplied in a sterile pack which should not be opened until required for insertion. The exposed product should be handled with aseptic precautions. If the seam of the sterile package is broken, the product should be discarded.

4.2.2 Additional information on special populations

4.2.2.1 Paediatric population

There is no relevant indication for the use of Mirena before menarche.

4.2.2.2 Geriatric patients

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

4.2.2.3 Patients with hepatic impairment

Mirena is contraindicated in women with acute liver disease or liver tumor (see Section 4.3).

4.2.2.4 Patients with renal impairment

Mirena has not been studied in women with renal impairment.

4.3 Contraindications

- Known or suspected pregnancy,
- Progestogen-dependent tumours, e.g. breast cancer
- Current or recurrent pelvic inflammatory disease
- Cervicitis
- Lower genital tract infection
- Postpartum endometritis
- Infected abortion during the past three months
- Conditions associated with increased susceptibility to infections
- Cervical dysplasia
- Uterine or cervical malignancy
- Undiagnosed abnormal uterine bleeding
- Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity
- Acute liver disease or liver tumour
- Hypersensitivity to levonorgestrel or to any of the excipients

4.4 Special Warnings and Precautions for Use

Use of Mirena in conjunction with an oestrogen for hormone replacement therapy.
In case Mirena is used in conjunction with an oestrogen for hormone replacement therapy, the safety information of the oestrogen applies in addition and should be followed.

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 ischemia
- Exceptionally severe headache
- Jaundice
- Marked increase in blood pressure
- Severe arterial disease such as stroke or myocardial infarction
- Acute venous thromboembolism

Mirena should be used with caution in postmenopausal women with advanced uterine atrophy.

Mirena may be used with caution in women who have congenital heart disease or valvular heart disease at risk of infective endocarditis. The need for antibiotic prophylaxis during insertion and removal of Mirena should be considered in patients with congenital or valvular heart disease. It is recommended that physicians consult local guidelines.

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.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst using Mirena.

Irregular bleedings may mask some symptoms and signs of endometrial polyps or cancer, and in these cases diagnostic measures have to be considered.

Since a biological effect of progestogens on liver cancer cannot be excluded, an individual benefit-risk assessment should be made in women with liver cancer.

Mirena does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Medical examination/consultation

Before insertion, the woman must be informed of the efficacy, risks including signs and symptoms of these risks as described in the Package Booklet and side effects of Mirena. A physical examination including pelvic examination and examination of the breasts should be conducted. Cervical smear should be performed as needed, according to Healthcare Professional's evaluation. Pregnancy and sexually transmitted diseases 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 maximize 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 (See Section 4.2). 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. Mirena must be inserted using aseptic technique.
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. See section 4.8.

The woman should be re-examined 4 to 12 weeks after insertion and once a year thereafter or more frequently if clinically indicated.

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

Oligo/amenorrhoea

Women of fertile age
Oligomenorrhoea and/or amenorrhoea develops gradually in 57% and 16% of women during the first year of use respectively. By the end of Year 6 of Mirena use, oligomenorrhea and amenorrhea are experienced by 31% and 24% 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 subjects unless indicated by other signs of pregnancy.

Because irregular bleeding/spotting is common during the first months of therapy, it is recommended to exclude endometrial pathology before insertion of Mirena.

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

If the woman continues the use of Mirena inserted earlier for contraception, endometrial pathology has to be excluded in case bleeding disturbances appear after commencing oestrogen replacement therapy.

If bleeding irregularities develop during prolonged treatment, appropriate diagnostic measures should also be taken.

Pelvic infection

A decision to use Mirena must include consideration of the risks of pelvic inflammatory diseases (PID).

The insertion tube helps to prevent Mirena from contamination with micro-organisms during the insertion and the Mirena inserter has been designed to minimise the risk of infections. In users of copper intrauterine devices (IUDs), the highest rate of pelvic infections occurs during the first month after insertion and decreases later.

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 gynecological or surgical procedures, severe infection or sepsis (including group A streptococcal sepsis) can occur following IUD insertion, although this is extremely rare.

Actinomycosis has been associated with IUDs. Symptomatic women should have the IUD removed and should receive antibiotics.

If the woman experiences recurrent endometritis or pelvic infections or if an acute infection is severe or does not respond to treatment within a few days, Mirena must be removed.
Bacteriological examinations are indicated and monitoring is recommended, even with discrete symptoms indicative of infections.

Signs and symptoms of PID should be investigated appropriately and treated promptly.

Expulsion

Symptoms of the partial or complete expulsion of any IUD may include bleeding or pain. However, the system can be expelled from the uterine cavity without the woman noticing it leading to 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.

After expulsion, Mirena may be replaced within 7 days from the onset of the next menstruation.

A displaced Mirena should be removed. A new 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 contraceptive may occur, most often during insertion, although it may not be detected until sometime later, and may decrease the effectiveness of Mirena. Such a system must be removed; 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.

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). 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=6047 insertions)	1.7 (95% CI 0.8-3.1; n=5927 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)

Extending the observational period to 5 years in a subgroup of this study (N = 39,009 women inserted with Mirena or copper IUD, 73% of these women had information available over the complete 5 years of follow-up), 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. Breastfeeding at the time of insertion and insertion up to 36 weeks after giving birth were confirmed as risk factors also in the subgroup that were followed up for 5 years.

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

Re-examination after insertion should follow the guidance given above under the heading "Medical examination/consultation" which may be adapted as clinically indicated in women with risk factors for perforation.

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

Breast cancer

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. 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.

Risk in post-menopausal women
The risk of breast cancer is increased in post-menopausal women using systemic (i.e. oral or transdermal) hormone replacement therapy (HRT). This risk is higher with combined oestrogen-progestogen HRT than with oestrogen only HRT. The product information of the oestrogen component of the treatment should also be consulted for additional information.

Ectopic pregnancy

Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry a higher risk of ectopic pregnancy. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrheic woman starts bleeding. The absolute risk of ectopic pregnancy with Mirena users is low due to the overall reduced likelihood of pregnancy in Mirena users compared to non-users of any contraception. In a large prospective comparative non-interventional cohort study with an observation period of 1 year, the ectopic pregnancy rate with Mirena was 0.02%. In clinical trials, the absolute rate of ectopic pregnancies with Mirena was approximately 0.1% per year, compared to 0.3-0.5% per year in women not using any contraception. However, if a woman becomes pregnant with Mirena in situ, the relative likelihood of this pregnancy being ectopic is increased.

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 drug reactions in approximately 7% of women using Mirena.
Most of these cysts 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.

Psychiatric disorders

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

4.5 Interaction with other Medicinal Products and other forms of Interaction

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

4.5.1 Effects of other medicinal products on Mirena

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 drugs on the 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 Pregnancy

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 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 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 closely monitored. 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 foetus 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.

4.6.2 Lactation

Levonorgestrel daily dose and blood concentrations are lower with Mirena than with any other hormonal contraceptive, although levonorgestrel has been identified in breast milk.
About 0.1 % of the levonorgestrel dose is transferred to the infant during breast-feeding. 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.

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

4.6.3 Fertility

Upon removal of Mirena, women return to their normal fertility. Clinical data from 310 women discontinuing use of Mirena for want of pregnancy has demonstrated a pregnancy rate of 79-96% after 12 months.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

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 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. By the end of Year 6 of Mirena use, prolonged bleeding and irregular bleeding are experienced by 2% and 15% of Mirena users, respectively; amenorrhea occurs in 24%, and infrequent bleeding in 31% of Mirena users.

When Mirena is used in combination with continuous oestrogen 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 drug reactions (ADRs) reported with Mirena are summarized in the table 2 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) and unknown. The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are crude incidences of the events observed in clinical trials in the indications contraception and idiopathic menorrhagia/ heavy menstrual bleeding, including 5091 women and 12,101 woman-years.

Adverse reactions in clinical trials in the indication protection from 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 drug reactions

System Organ Class	Very Common	Common	Un-common	Rare	Unknown
Immune system disorders					Hypersensitivity including rash, urticaria and angioedema

Psychiatric disorders		Depressed mood/ Depression, Libido decreased			
Nervous system disorders	Headache	Migraine			
Vascular disorders		Dizziness			
Gastrointestinal disorders	Abdominal/ pelvic pain	Nausea			
Skin and subcutaneous tissue disorders		Acne Hirsutism	Alopecia Chloasma/ skin hyper-pigmentat-ion		
Musculoskeletal, connective tissue and bone disorders		Back pain**			
Reproductive system and breast disorders	Bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorr-hoea and amenorrhoea Vulvovaginitis* Genital discharge*	Upper genital tract infection Ovarian cyst Dysmenorrhea Breast pain** Intra-uterine contraceptive device expelled (complete and partial)	Uterine perforation ***		
Investigations		Weight increase			Blood pressure increased

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

*Endometrial protection trials: "common"

** Endometrial protection 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). In clinical trials with Mirena that excluded breastfeeding women the frequency of perforation was "rare".

Infections and Infestations
Cases of sepsis (including group A streptococcal sepsis) have been reported following IUD insertion (see section 4.4).

4.8.3 Description of selected adverse reactions

Pregnancy, puerperium and perinatal conditions:

When a woman becomes pregnant with Mirena in situ, the relative risk of ectopic pregnancy is increased (see Section 4.4).

Reproductive system and breast disorders:

Cases of breast cancer have been reported (frequency unknown, see Section 4.4).

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Not relevant.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

ATC code: G02BA03

Pharmacotherapeutic group: Plastic IUD with Progestogen

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

Mirena has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentration in the endometrium down-regulates 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 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 contraceptive efficacy of Mirena has been studied in 5 major clinical studies with 3330 women using Mirena. The Pearl Index was approximately 0.2 at 1 year and the cumulative failure rate was approximately 0.7% at 5 years. The contraceptive efficacy of Mirena beyond 5 years has been studied in a clinical study with 362 women using Mirena. During year 6 of Mirena use, the Pearl Index was 0.35 [95% CI (0.01; 1.95)].

Table 3 Cumulative Failure Rate (%) and Pearl Index

Year	Cumulative Failure Rate (%)*	Pearl Index
Contraceptive Efficacy during Years 1 to 5 (N= 3330, Pooled data of contraceptive trials up to 5 years)		
Year 1	0.20	0.21
Years 1 to 5	0.71	
Contraceptive Efficacy beyond 5 years (N=362, Mirena Extension Trial)		
Year 6	0.29	0.35

*Kaplan Meier method

The failure rates also include 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 women wishing to become pregnant conceived within 12 months after removal of the system.

The menstrual pattern is a result of the direct action of levonorgestrel on the endometrium and does not reflect the ovarian cycle. There is no clear difference in follicle development, ovulation or estradiol and progesterone production in women with different bleeding patterns. 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. Scanty flow frequently develops into oligomenorrhoea and amenorrhoea. Ovarian function is normal and estradiol levels are maintained, even when users of Mirena are amenorrhoeic.

Mirena can be successfully used in the treatment of idiopathic menorrhagia. 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. Menorrhagia caused by submucosal fibroids may respond less favorably. Reduced bleeding increases the concentration of blood hemoglobin. Mirena also alleviates dysmenorrhoea.

The efficacy of Mirena in preventing endometrial hyperplasia during continuous oestrogen treatment has been equally good when administering oestrogen either orally or transdermally. The observed hyperplasia rate under oestrogen therapy alone is as high as 20%. 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.

5.2 Pharmacokinetic Properties

The active ingredient of Mirena is levonorgestrel. Levonorgestrel is directly released into the uterine cavity. Estimated *in vivo* release rates for different points in time are provided in table 4.

Table 4: Estimated *in vivo* release rates for Mirena:

Time	Estimated *in vivo* release rate [micrograms/24 hours]
Initial	20
1 year after insertion	18
5 years after insertion	10

6 years after insertion	9
Average over 5 years	15
Average over 6 years	15

Absorption

Following insertion, levonorgestrel is released 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 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 pg/ml (25^{th} to 75^{th} percentiles: 151 pg/ml to 264 pg/ml) at 6 months to 194 pg/ml (146 pg/ml to 266 pg/ml) at 12 months, and to 131 pg/ml (113 pg/ml to 161 pg/ml) at 60 months in women of reproductive age weighing above 55 kg. After 72 months (6 years) median levonorgestrel concentration amounted to 113 pg/ml (87.3 pg/ml to 155 pg/ml).

The high local drug exposure in the uterine cavity leads to a strong concentration gradients 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 oestrogen treatment, the median serum concentration of levonorgestrel declines from 257 pg/ml (25^{th} to 75^{th} percentiles: 186 pg/ml to 326 pg/ml) at 12 months to 149 pg/ml (122 pg/ml to 180 pg/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 pg/ml (25^{th} to 75^{th} percentiles: 341 pg/ml to 655 pg/ml) due to the induction of SHBG by oral oestrogen treatment.

Distribution

Levonorgestrel is bound non-specifically to serum albumin and specifically to the Sex Hormone-Binding Globulin (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 month after insertion of Mirena, remained stable during the first year and increased slightly thereafter. During Year 6 of use SHBG concentration remained stable. 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.

Biotransformation

Levonorgestrel is extensively metabolized. 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. CYP3A4 is the main enzyme involved in the oxidative metabolism of LNG. The available in vitro data suggest that CYP mediated biotransformation reactions may be of minor relevance for LNG compared to reduction and conjugation.

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. 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

The preclinical safety evaluations revealed no special hazard for humans based on studies of safety pharmacology, pharmacokinetics, toxicity, genotoxicity and carcinogenic potential of levonorgestrel. Levonorgestrel is a well-established progestogen with anti-oestrogenic 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 safety evaluation of the elastomer components of the hormone reservoir, polyethylene materials of the product, and combination of elastomer and levonorgestrel, based on both the assessment of genetic toxicology in standard in vitro and in vivo test systems and on biocompatibility tests in mice, rats, guinea pigs, rabbits and in vitro test systems has not revealed bio-incompatibility.

6. Pharmaceutical Particulars

6.1 List of Excipients

Polydimethylsiloxane elastomer
Polydimethylsiloxane tubing
Polyethylene
Barium sulphate
Iron oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Three years

6.4 Special Precautions for Storage

Store in the original package to protect from moisture and direct sunlight.

6.5 Nature and Contents of Container

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

6.6 Instructions for Use and Handling

Mirena is supplied in a sterile pack which should not be opened until required for insertion. The exposed product should be handled with aseptic precautions. If the seam of the sterile envelope is broken, the product inside should be discarded. Special instructions for insertion are in the package. For further information see also Section 4.2, Posology and Method of Administration, Insertion and removal/replacement.

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

7. Marketing Authorisation Holder

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18

Ireland

8. Marketing Authorisation Number

PA 1410/008/001

9. Date of First Authorisation/Renewal of Authorisation

Date of first authorisation: 28 August 1998
Date of last renewal: 28 August 2008

10. Date of Revision of the Text

February 2021