SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mirena 20 micrograms/24 hours intrauterine delivery system

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One intrauterine delivery system contains 52 mg of levonorgestrel. The average *in vivo* release rate is approximately 20 micrograms per 24 hours during the first year.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intrauterine delivery system (IUS)

The IUS consists of a white or almost white hormone-elastomer core covered with a semi-opaque membrane, which is mounted on the vertical stem of a T-body. The white T-body has a loop at one end and two horizontal arms at the other end. Two 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 IUS is inside the insertion tube. The IUS is free of impurities.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception, idiopathic menorrhagia/hypermenorrhea, dysmenorrhea, and local progestogen treatment during estrogen replacement therapy.

4.2 Posology and method of administration

Mirena is inserted into the uterine cavity. It is effective for 8 years in the indication of contraception and 5 years in the indications of idiopathic menorrhagia/hypermenorrhea, dysmenorrhea, and local progestogen treatment during estrogen replacement therapy. For timing regarding removal/replacement, see section Removal/replacement.

<u>Insertion</u>

Mirena should only be inserted by healthcare professionals who are experienced in Mirena insertions or have undergone sufficient training for Mirena insertion.

Before insertion, the patient should be carefully examined to detect any contraindication to IUS insertion. Exclude pregnancy before insertion. Consider the possibility of ovulation and conception before using this product. Mirena is not suitable for use as a postcoital contraceptive (see sections 4.3 and 4.4 under “Medical examination and precautions”).

Table 1: When to insert Mirena in women of fertile age

Starting Mirena	• Mirena should be inserted into the uterine cavity within 7 days of the onset of menstruation. In this case, Mirena provides contraceptive protection upon insertion and no back-up contraception is needed. • If insertion within 7 days of the onset of menstruation is not possible or the woman experiences irregular menses, Mirena may be inserted at any time during the menstrual cycle provided that the healthcare professional can reliably exclude the possibility of prior conception. However, in this case immediate contraceptive protection upon insertion is not ensured. Therefore, a barrier method of contraception should be used or the patient should abstain from vaginal intercourse for the next 7 days to prevent pregnancy.
Postpartum insertion	In addition to the instructions above (Starting Mirena): Postpartum insertions should be postponed until the uterus is fully involuted, and insertion should not be performed earlier than 6 weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum.
Insertion after first-trimester abortion	Mirena can be inserted immediately after first-trimester abortion. In this case, no back-up contraception is needed.
Replacing Mirena	Mirena can be replaced by a new system at any time in the menstrual cycle. In this case, no back-up contraception is needed.
Changing from another contraceptive method (e.g., combined hormonal contraceptives, implant)	• Mirena can be inserted immediately if it is reasonably certain that the woman is not pregnant. • Need for back-up contraception: If it has been more than 7 days since menstrual bleeding began, the woman should abstain from vaginal intercourse or use additional contraceptive protection for the next 7 days.

Important information to consider during or after insertion

In case of a difficult insertion or exceptional pain or bleeding during or after insertion, the possibility of perforation of the uterine wall should be considered and excluded by taking appropriate steps, such as pelvic examination and ultrasound.

After insertion, women should be re-examined after 4 to 12 weeks to check the threads and ensure that the IUS is in the correct position. A pelvic examination alone (including checking of threads) may not be sufficient to exclude partial perforation of the uterine wall and ultrasound may be considered (see section 4.4).

Mirena is not intended for use as a postcoital contraceptive.

Mirena in the treatment of idiopathic menorrhagia/hypermenorrhea and dysmenorrhea

Mirena is inserted into the uterine cavity during menstrual bleeding, within seven days of the onset of menstruation. Mirena can be replaced by a new system at any time in the cycle.

Mirena as local progestogen treatment during estrogen replacement therapy

In women using Mirena as part of their hormone replacement therapy, it can be used in combination with oral or transdermal estrogen therapy. Because spotting is common during the first months of therapy, a sample should be taken from the uterine cavity to check the endometrium before insertion of Mirena. If the woman continues the use of Mirena as part of hormone replacement therapy when there is no longer need for contraception, an endometrial sample has to be taken in case bleeding appears after commencing estrogen therapy or develops later during therapy. Mirena can be inserted at any time in amenorrheic women, or during menstruation or withdrawal bleeding if they still occur.

In the treatment of menorrhagia and in local progestogen treatment in conjunction with estrogen replacement therapy Mirena releases a sufficient amount of levonorgestrel during a five-year period to prevent proliferation of the endometrium. When Mirena is replaced with a new system, it can be inserted immediately into the uterine cavity.

Removal/replacement

Contraception: When used for contraception, Mirena must be removed or replaced with a new system after eight years.

Continuation of contraception after removal

- If the user wishes to continue using the same method, a new system can be inserted at the time of removal.
- If the user does not wish to continue using the same method but pregnancy is not desired, the removal should be carried out within seven days of the onset of menstruation in women of fertile age, provided that the woman is still experiencing regular menses. If the system is removed at some other time during the cycle or the woman does not experience regular menses and the patient has had intercourse within a week prior to removal, she is at risk of pregnancy. To ensure continuous contraception, a barrier contraceptive method (such as condoms) should be used starting at least 7 days before the removal. After removal, the new contraceptive method should be started immediately (follow the instructions for use of the new contraceptive method).

Idiopathic menorrhagia/hypermenorrhea and dysmenorrhea: Mirena must be removed or replaced with a new system in case symptoms of idiopathic menorrhagia/hypermenorrhea or dysmenorrhea return. If symptoms have not returned after five years of use, continued use of Mirena may be considered. Remove or replace Mirena eight years after insertion at the latest.

Local progestogen treatment in conjunction with estrogen replacement therapy: Mirena must be removed or replaced with a new system after five years.

Mirena is removed by gently pulling on the threads with forceps. The use of excessive force or sharp instruments during removal may cause breakage of the system. After removal of Mirena, the system should be examined to ensure that it is intact and has been completely removed. 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 the removed IUS has been ascertained to be otherwise intact. The knobs at the end of the horizontal arms usually prevent complete detachment of the hormone cylinder from the T-body. If the threads are not visible, the location of the system must be determined via ultrasound or other method. If the system is in the uterine cavity, it may be removed using narrow forceps. This may occasionally require dilatation of the cervical canal or other surgical intervention. Insertion and removal may be associated with short-term pain and bleeding. The procedure may precipitate a vasovagal reaction or a seizure in an epileptic patient.

Instructions for handling and use

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

Mirena is supplied with a patient reminder card in the outer carton. Complete the patient reminder card and give it to the patient after insertion.

Pediatric population

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

4.3 Contraindications

- Known or suspected pregnancy
- Progestogen-dependent tumors, e.g. breast cancer
- Acute or recurrent pelvic inflammatory disease
- Cervicitis
- Lower genital tract infection
- Postpartum endometritis
- Infected miscarriage or abortion during the past three months
- Increased susceptibility to infections
- Cervical dysplasia
- Confirmed or suspected uterine or cervical malignancies
- Undiagnosed abnormal uterine bleeding
- Congenital or acquired uterine anomaly, including fibroids if they distort the uterine cavity
- Acute liver disease or liver tumor
- 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 system should be considered if any of the following conditions 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 cerebrovascular accident or myocardial infarction
- Acute venous thromboembolism.

Appropriate diagnostic and therapeutic measures should be undertaken immediately if there are symptoms indicating retinal thrombosis, such as unexplained partial or complete loss of vision, proptosis or diplopia, papilledema, or retinal vascular lesions.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in thromboembolism. Mirena may be used with caution in women who have congenital heart disease or valvular heart disease and are at risk of contracting infectious endocarditis.

Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of Mirena. However, there is usually no need to adjust the treatment in diabetic users of Mirena.

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

Mirena is not the method of first choice for postmenopausal women with advanced uterine atrophy.

When Mirena is used concomitantly with estrogen in hormone replacement therapy, the safety data relevant to estrogens should also be considered.

Medical examination and precautions

Before insertion, the woman must be informed of the efficacy, risks (including the signs and symptoms of risks described in the package leaflet) and adverse effects of Mirena. A pelvic examination, examination of the breasts, and a cervical smear if not taken within three months, should be performed before insertion. Pregnancy and sexually transmitted diseases should be excluded. Genital infections have to be successfully treated prior to insertion. The position of the uterus and the size of the uterine cavity should be determined. Fundal positioning of Mirena is important in order to ensure uniform exposure of the uterus to the progestogen. The risk of expulsion will then also be low and the contraceptive efficacy is maximized. It is important that the instructions for insertion are followed carefully. Since the insertion technique of Mirena is different from other intrauterine devices, special emphasis should be given to training in the correct insertion technique. Insertion and removal may be associated with short-term pain and bleeding. The procedure may precipitate fainting as a vasovagal reaction, or a seizure in an epileptic patient. If an insertion is expected to be associated with problems and/or severe pain, use of a system with an insertion tube with a smaller diameter should be considered.

The woman should be re-examined 4 to 12 weeks after insertion. Vaginal ultrasound examination may be considered to ascertain the correct position of the system. In case Mirena cannot be located in the uterine cavity, the possibility of expulsion or complete perforation should be considered (see section "Perforation" below) and X-ray may be used. Thereafter, re-examination should be performed once a year or more frequently if clinically indicated.

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

Since irregular bleeding and spotting are common during the first months of therapy, endometrial pathology should be excluded before the insertion of Mirena. If the woman continues the use of Mirena as part of hormone replacement therapy when there is no longer need for contraception, required diagnostic measures have to be taken in case bleeding appears after commencing estrogen replacement therapy. If bleeding irregularities develop during a prolonged treatment, appropriate diagnostic measures should also be taken.

Perforation

Perforation or penetration of the uterine corpus or cervix by an intrauterine contraceptive may occur, most often during insertion, and it may not be detected until later. A system located outside the uterus has reduced contraceptive efficacy. In some cases, the device may be located outside of the uterine cavity. Such a system must be removed. Surgery may be required.

In a large prospective non-interventional cohort study in users of intrauterine contraceptive (n = 61,448 women), the incidence of perforation during a 1-year observational period was 1.3 (95% CI: 1.1–1.6) per 1000 insertions in the entire study cohort, 1.4 (95% CI: 1.1–1.8) per 1000 insertions in the Mirena cohort, and 1.1 (95% CI: 0.7–1.6) per 1000 insertions in the copper IUD cohort.

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

factors were independent of the type of intrauterine contraceptive inserted.

Table 2: Incidence of perforation per 1000 insertions for the entire study cohort observed over 1 year, stratified by breastfeeding and time since delivery at insertion

	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 = 41910 insertions)

When the observational period was extended to 5 years in a subgroup of this study (n = 39,009 women using Mirena or copper IUD; for 73% of these women the data were available for the entire observational period), the incidence of perforation detected at any time during the 5-year period was 2.0 (95% CI: 1.6–2.5) per 1000 insertions. Insertion during breastfeeding and up to 36 weeks after giving birth were confirmed as risk factors also in the subgroup 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 under the heading "Medical examination and precautions", including the consideration to use vaginal ultrasound examination diagnosis to ascertain the correct position of the system 4 to 12 weeks after insertion. The guidance 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, 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 retrieved from the cervical canal with a suitable instrument. If they cannot be found, the possibility of expulsion or perforation should be considered. Vaginal ultrasound examination may be used to ascertain the position of the system. If ultrasound is not available or successful, X-ray may be used to locate Mirena.

Oligomenorrhea and amenorrhea

In women of fertile age, oligomenorrhea and amenorrhea develop gradually in about 57% and 16% of women, respectively, during the first year of use. By the end of year 8 of Mirena use, oligomenorrhea and amenorrhea are experienced by 26% and 34% of Mirena users, respectively. The possibility of pregnancy should be excluded if menstruation does not occur within six weeks of the onset of the previous menstruation, and a check should be made to ensure that the system is still in place. A repeated pregnancy test is not necessary in patients who remain amenorrheic unless indicated by other signs of pregnancy.

Due to the strong local effect levonorgestrel has on the endometrium, the endometrial lining does not react to estrogen and, therefore, proliferation does not occur. The duration and volume of menstrual bleeding is reduced. When women with different bleeding patterns were compared, no clear difference in follicle development, ovulation or estradiol or progesterone production was found. In menorrhagic women, the volume of menstrual bleeding decreased by 62–94% during the first three months of use and 71–95% during the first six months of use. Reduced bleeding increases the hemoglobin level. When local progestogen treatment is used in combination with estrogen therapy, amenorrhea gradually develops in most women during the first year. Irregular bleeding and spotting were fairly common during the first three months of use.

Pelvic infections

The insertion tube helps to protect Mirena from contamination with micro-organisms during the insertion, and the inserter has been designed to minimize the risk of infections. Based on the experience obtained from users of copper intrauterine devices, the risk of infection is highest during the first month of use and decreases later. The risk of infection is highest in young women or if the woman or her partner have multiple sexual partners. A pelvic inflammatory disease 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.

If an acute infection does not respond to treatment within a few days, or if the patient experiences recurrent endometritis or other pelvic infections, Mirena must be removed (see section 4.3). Some studies indicate that the rate of pelvic infections in users of Mirena is lower than in users of copper-releasing intrauterine devices.

Bacteriological examinations are indicated and monitoring is recommended, even with mild symptoms indicative of infections.

Expulsion

In clinical trials with Mirena in the contraception indication, the incidence of expulsion was low (<4% of insertions) and in the same range as reported for other IUDs and IUSs.
Symptoms of partial or complete expulsion of Mirena 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. As Mirena normally decreases menstrual flow, an increase in menstrual flow may be indicative of an expulsion.

The risk of expulsion is increased in

- women with history of heavy menstrual bleeding (including women who use Mirena for the treatment of heavy menstrual bleeding)
- women with a higher than normal BMI at the time of insertion; this risk increases gradually with increasing BMI.

Women should be counselled on possible symptoms of expulsion and how to check the threads of Mirena and advised to contact a healthcare professional if the threads cannot be felt. A barrier contraceptive (such as a condom) should be used 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.

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 estrogen-progestogen preparations. The excess risk gradually disappears during the course of 10 years after cessation of COC use. Since 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 users of progestogen-only oral contraceptives (OCs) is possibly of similar magnitude to that associated with COCs. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and is so less conclusive than that for COCs. These studies do not provide evidence for causality. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both. The breast cancers diagnosed in women using COCs continuously tend to be less advanced clinically than the cancers diagnosed in women who have never used COCs.

The risk of breast cancer is increased in menopausal women using systemic hormone replacement therapy (tablets or a preparation applied on the skin). The risk is higher in users of the combination of estrogen and progestogen than in users of estrogen only. The product information on the estrogen preparation used in the treatment must also be read through.

Ectopic pregnancy

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

Ovarian cysts

Since Mirena has a mainly local mechanism of action, ovulatory cycles with follicular rupture usually occur normally 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 the 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 2 to 3 months. Should this not happen, ultrasound monitoring and other diagnostic/therapeutic measures based on the findings are recommended. Surgical intervention is required rarely.

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 behavior and suicide. Women should be advised to contact a healthcare professional in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Precautions at time of removal

The use of excessive force or sharp instruments during removal may cause breakage of the system (see section 4.2). After removal of Mirena, the system should be examined to ensure that it is intact and has been completely removed.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions can occur with drugs that induce liver enzymes, which can result in increased 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 herbal preparations containing St. John's wort (*Hypericum perforatum*).

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

Substances with variable effects on the clearance of levonorgestrel, e.g.:

When co-administered with sex hormones, many anti-HIV 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):

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

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, the system should be removed as soon as possible, since any intrauterine contraceptive left in situ may increase the risk of abortion and preterm labor. Removal of Mirena may also 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, such as cramping abdominal pain with fever.

In addition, an increased risk of virilizing effects in a female fetus because of the intrauterine exposure to levonorgestrel cannot be excluded. There have been isolated cases of masculinization of the external genitalia of the female fetus following local exposure to levonorgestrel during pregnancy with a hormonal IUS in place.

Breastfeeding

The daily dose and the plasma concentrations of levonorgestrel are lower with Mirena than with any other hormonal contraceptive method but levonorgestrel has been identified in breast milk. About 0.1% of the levonorgestrel dose is transferred to the infant during breastfeeding. Hormonal contraceptives are not recommended as the method of first choice during lactation, but progestogen-only methods are considered the second choice after non-hormonal contraceptive methods.

There appears to be no deleterious effects on infant growth or development when using any progestogen-only method after six weeks postpartum. Progestogen-only methods do not appear to affect the quantity or quality of breast milk.

Fertility

Upon removal of Mirena, women return to their normal fertility.

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

Subjective undesirable effects may occur during the first months after insertion but they usually subside during prolonged use. In addition to the adverse effects listed in section 4.4, the following undesirable effects have been reported in users of Mirena.

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

In women of fertile age, the number of spotting days per month decreases gradually from nine to four during the first six months of use. After the first month of use, 20% of users experience prolonged bleeding (more than eight days). For many women, periods become shorter after this, and after three months of use only 3% of users experience prolonged bleeding. In clinical trials during the first year of use, 17% of women experienced amenorrhea for a period of at least three months. By the end of year 8 of Mirena use, prolonged bleeding and irregular bleeding are experienced by 3% and 10% of Mirena users, respectively; amenorrhea occurs in 34%, and infrequent bleeding in 26% of Mirena users.

When Mirena is used as local progestogen therapy in combination with estrogen replacement therapy, most women experience spotting or irregular bleeding during the first months of the treatment. Bleeding and spotting decrease gradually, and in about 40% of the users the periods stop completely within the last three months of the first year of use. Bleeding disorders were more common in perimenopausal women than in postmenopausal women.

The frequency of benign ovarian cysts depends on the diagnostic method used, and they have been diagnosed in 7% of the users as adverse effects. Most of the follicles are asymptomatic and disappear spontaneously within three months.

Table 3 below presents a summary of adverse reactions by MedDRA system organ classes. The frequencies are based on clinical trial data.

Table 3: Adverse drug reactions

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Psychiatric disorders		Depressed mood/ depression Nervousness Decreased libido		
Nervous system disorders		Headache	Migraine	
Vascular disorders		Dizziness		
Gastrointestinal disorders		Abdominal pain Nausea	Abdominal distension	
Skin and subcutaneous tissue disorders		Acne	Alopecia Hirsutism Pruritus Eczema Chloasma/skin hyperpigmentation	Rash Urticaria
Musculoskeletal and connective tissue disorders		Back pain		
Reproductive system and breast disorders	Benign ovarian cysts Uterine/vaginal bleeding, including spotting, oligomenorrhea, amenorrhea	Pelvic pain Dysmenorrhea Vaginal discharge Vulvovaginitis Breast tenderness Breast pain Expulsion of the intrauterine contraceptive	Uterine perforation* Pelvic inflammatory disease Endometritis Cervicitis / Pap smear normal, class II	
General disorders and administration site conditions			Edema	
Investigations		Weight increase		

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

* This frequency is based on a large prospective non-interventional cohort study 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). The frequency of perforation was "rare" in clinical trials with Mirena that excluded breastfeeding women.

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.

Infections

Cases of sepsis (including group A streptococcal sepsis) have been reported following insertion of intrauterine contraceptives (see section 4.4).

Pregnancy, puerperium and perinatal conditions

If a woman becomes pregnant with the IUS in situ, the relative risk of ectopic pregnancy is increased (see section 4.4).

Reproductive system and breasts

Cases of breast cancer have also been reported in connection with the use of the IUS (frequency unknown; see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 to the following address:

website: www.fimea.fi
Finnish Medicines Agency Fimea
Lääkkeiden haittavaikutusrekisteri [*register of adverse drug reactions*]
PL 55
00034 FIMEA

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Plastic IUD with progestogen
ATC code: G02BA03

Levonorgestrel is a progestogen with antiestrogenic activity used in gynecology in various ways: as the progestogen component in hormonal therapy and in combined oral contraceptives and alone in the so-called 'minipills' and subdermal implants. Mirena releases levonorgestrel directly into the uterus. This allows a very low daily dosage, as the hormone is released directly into the target organ. The plasma concentrations of levonorgestrel are thus lower than with any other contraceptive method.

Mirena has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentrations in the endometrium prevent the synthesis of endometrial estrogen and progesterone receptors, making the endometrium insensitive to estrogen and producing an antiproliferative effect. Morphological changes of the endometrium and a weak local foreign body reaction are observed during the use of Mirena. Thickening of the cervical mucus prevents passage of the sperm through the cervical canal. In addition, the local milieu of the uterus and the ovarian tubes strongly inhibits sperm mobility and function, preventing fertilization. Ovulation is inhibited in some women.

The contraceptive efficacy of Mirena has been studied in five major clinical studies with 3,330 women using Mirena. The contraceptive efficacy of Mirena beyond 5 years has been studied in 362 women in a clinical trial 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; 1.00)]. The contraceptive efficacy of Mirena is summarized in Table 4.

Table 4: Cumulative failure rate (%) and Pearl Index

Year	Cumulative failure rate (%)* (95% confidence interval)	Pearl Index (95% confidence interval)
Contraceptive efficacy during Years 1 to 5 (N= 3,330, Pooled data of contraceptive trials up to five years)		
Year 1	0.20 (0.09; 0.46)	0.21 (0.08; 0.45)
Years 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)
Years 6 to 8	0.68 (0.17; 2.71)	0.28 (0.03; 1.00)

* Kaplan-Meier method

The failure rate also includes pregnancies occurring after undetected expulsions and perforations. Similar contraceptive efficacy has been observed in a large post-marketing study with 17,000 women using Mirena. Because the use of Mirena does not require daily intake compliance, the pregnancy rates in "typical use" are similar to those observed in controlled clinical trials (perfect use).

When toleration is measured by continuation rate, the Mirena method has been as well tolerated in contraceptive use as copper intrauterine devices. The continuation rate after the first year of use is approximately 80%.

The use of Mirena does not alter the course of future fertility. After removal of the system, fertility returns to the same level as in women using no contraception. About 80% of the women who had their Mirena removed because they wished to become pregnant conceived within 12 months after the removal.

The menstrual pattern is a result of the direct action of levonorgestrel on the endometrium, and it is not regulated by the ovarian function. There is no 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 in spotting during the first months of use. Thereafter, the strong suppression of the endometrium results in reduction of the duration and volume of menstrual bleeding during the use of Mirena. Scanty flow frequently develops into oligomenorrhea or amenorrhea. Ovarian function is normal and estradiol levels are maintained, even when users of Mirena are amenorrheic.

Mirena has been developed especially for women requiring long-term, effective contraception. It can also be successfully used in the treatment of menorrhagia. In menorrhagic women, the volume of menstrual bleeding decreases by 62–94% during the first three months of use and 71–95% during six months of use. Compared to endometrial ablation or resection, Mirena is equally effective in reducing the menstrual blood loss for up to two years. Reduced bleeding increases the hemoglobin level. Menorrhagia caused by submucosal fibroids may respond less favorably. Like oral contraceptives, Mirena also alleviates dysmenorrhea.

The effect of Mirena in the treatment of menorrhagia and in local progestogen treatment in conjunction with estrogen replacement therapy is based on the action levonorgestrel exerts on the endometrium, preventing endometrial proliferation. No endometrial hyperplasias were reported during a 12-month study. Similar prevention of proliferation has been achieved in patients using estrogen orally, transdermally or subcutaneously. The amount of levonorgestrel released by Mirena is sufficient to prevent endometrial proliferation for five years.

Mirena has been equally effective in preventing endometrial hyperplasia as estrogen used either orally or transdermally. The observed frequency of hyperplasia during estrogen-only therapy has been up to 20%. In clinical trials with a total of 634 perimenopausal and postmenopausal users of Mirena, no hyperplasia was reported during the observation period ranging from one to five years.

5.2 Pharmacokinetic properties

Levonorgestrel is released locally into the uterine cavity. Estimated *in vivo* release rates for different time points are provided in Table 5.

Table 5: Estimated *in vivo* release rates for Mirena

Time	Estimated *in vivo* release rate [microg/24 hours]
24 days after insertion	21
60 days after insertion	21
1 year after insertion	19
3 years after insertion	14
5 years after insertion	11
8 years after insertion	7
Average over 1 years	20
Average over 3 years	18
Average over 5 years	15
Average over 8 years	13

Absorption

Following insertion, levonorgestrel is released into the uterine cavity without delay based on serum concentration measurements. The released levonorgestrel is fully systemically available.

After insertion of Mirena, levonorgestrel is detectable in serum/plasma after 1 hour. The maximum concentration of 180 ng/l (coefficient of variation, CV 38.3%). is reached within 2 weeks after insertion. In correspondence with the declining release rate, the serum/plasma concentration of levonorgestrel (geometric mean) declines continuously, as shown in table 6.

Table 6: Total levonorgestrel concentrations in plasma

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

The high local drug exposure in the uterine cavity is important for the local effect of Mirena on the endometrium, and it 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 > 1,000-fold).

Because of the low drug levels in plasma, the systemic effects of the progestogen are minimal.

Distribution

The pharmacokinetics of levonorgestrel have been extensively studied and reported in the literature. Orally administered levonorgestrel is rapidly and completely absorbed and the absolute bioavailability is about 90%. Levonorgestrel is bound non-specifically to serum albumin and specifically to sex hormone binding globulin (SHBG). Less than 2% of the total levonorgestrel concentration in serum 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 declines on average by about 20% during the first two months after insertion of Mirena and remains stable thereafter, increasing only slightly by the end of the 8 years of use.

The mean apparent volume of distribution of levonorgestrel is about 106 liters.

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 the levonorgestrel concentration. In women of reproductive age with low body weight (37–55 kg) the median serum concentration of levonorgestrel is about 1.5-fold higher than normal.

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

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. In addition, CYP3A4 is involved in the oxidative metabolism of levonorgestrel. The available *in vitro* data suggest, however, that this metabolic pathway is of minor relevance 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. Metabolites are excreted with feces and urine in equal amounts. The half-life, which is mainly represented by metabolites, is about one day.

Linearity/non-linearity

The pharmacokinetics of levonorgestrel are 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

Study data revealed no special hazard for humans based on conventional studies of safety pharmacology, pharmacokinetics and toxicity, including genotoxicity, and carcinogenic potential of levonorgestrel. Levonorgestrel is a widely-used progestogen with known antiestrogenic 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 and polypropylene materials of the product and the combination of elastomer and levonorgestrel, based on both the assessment of genetic toxicology in *in vitro* and *in vivo* test systems and biocompatibility tests in mice, rats, guinea pigs, rabbits and in vitro test systems have not revealed bioincompatibility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hormone-elastomer core:	polydimethylsiloxane, silica
T-body:	polyethylene, barium sulphate
Removal thread:	polyethylene, iron oxide (E 172)

6.2 Incompatibilities

Not relevant.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The IUS is a T-shaped structure with a matrix containing the hormone around the vertical stem of the polyethylene body. The vertical stem of the IUS is inside the insertion tube and the horizontal arms are freely visible.

<u>Mirena intrauterine delivery system in an inserter:</u>
The package contains one intrauterine delivery system and an inserter. The inserter components are the insertion tube, plunger, flange, slider and body. The product is packed into a formed blister package. The clear film is APET or PETG plastic and the white film is polyethylene.

Mirena intrauterine delivery system in an insertion tube:
The package contains one intrauterine delivery system and an insertion tube. The insertion tube components are the insertion tube, flange and plunger. The product is packed into a pouch that can be ripped open. The white side of the pouch is PE plastic, and the transparent side is film made of PE/PET plastic.

Not all pack types may be marketed.

6.6 Special precautions for disposal and other handling

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

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

7. MARKETING AUTHORIZATION HOLDER

Bayer Oy, Pansiontie 47, 20210 Turku

8. MARKETING AUTHORIZATION NUMBER

10212

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization: 9 May 1990
Date of latest renewal: 16 June 2008

10. DATE OF REVISION OF THE TEXT

28 March 2025