1. NAME OF THE MEDICINAL PRODUCT

Mirena 20 micrograms/24 hours intrauterine delivery system

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Levonorgestrel 52 mg. The average in vivo release rate is 20 micrograms /day during the first year.

For a full list of excipients, see section 'List of excipients'.

3. PHARMACEUTICAL FORM

Intrauterine delivery system (IUS).

The levonorgestrel (LNG) IUS consists of a white or almost white drug core covered with an opaque membrane, which is mounted on the vertical stem of a T-body. The 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 IUS is loaded in the insertion tube at the tip of the inserter. The IUS and inserter are essentially free of visible impurities.

4. CLINICAL PARTICULARS

4.1 Indication(s)

Contraception. Idiopathic menorrhagia. Mirena may be particularly useful in women with idiopathic menorrhagia requiring (reversible) contraception. Protection from endometrial hyperplasia during oestrogen replacement therapy.

4.2 Dosage and method of administration

4.2.1 Method of administration

Mirena is inserted into the uterine cavity. It is effective for 8 years for contraception and for 5 years in the indications idiopathic menorrhagia and protection from endometrial hyperplasia during estrogen replacement therapy

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 5 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 hormonal replacement therapy, Mirena can be used in combination with oral or transdermal estrogen preparations without progestogens.

The contraceptive efficacy of Mirena up to 8 years, when inserted according to the insertion instructions, is presented in table 1 below.

Table 1 Contraceptive efficacy

Contraceptive Efficacy within the first 5 years (N= 3330, Pooled data of contraceptive trials up to 5 Years)	
Year 1 Pearl Index	0.2
Years 1-5 cumulative failure rate (%)*	**0.7**
Contraceptive Efficacy beyond 5 years (N=362, Mirena Extension Trial)	
Year 6 Pearl Index	0.34
Year 7 Pearl Index	0.40
Year 8 Pearl Index	0.00
Years 6-8 cumulative failure rate (%)*	**0.68**

* Kaplan-Meier estimate

- Insertion and removal/replacement

Insertion

In women of fertile age, Mirena is to be inserted into the uterine cavity within seven days of the onset of menstruation.

Mirena can be replaced by a new system at any time in the cycle. The system can also be inserted immediately after first trimester abortion.

Postpartum insertions should be postponed until the uterus is fully involuted, however not earlier than six weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum. In case of a difficult insertion and/or exceptional pain or bleeding during or after insertion the possibility of perforation should be considered and appropriate steps should be taken, such as physical examination and ultrasound.

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

It is recommended that Mirena should only be inserted by physicians/health care professionals who are experienced in Mirena insertions and/or have undergone sufficient training for Mirena insertion.

Removal/Replacement

Contraception
The system should be removed or replaced after 8 years.

If pregnancy is not desired, the removal should be carried out within 7 days of the onset of menstruation in women of fertile age, provided the woman is 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 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 contraceptive method should have been initiated.

Idiopathic menorrhagia
The system should be removed or replaced in case symptoms of idiopathic menorrhagia 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.

Mirena is removed by gently pulling on the threads with forceps. The use of excessive force during removal may cause damage to the device. After removal of Mirena, the system should be examined to ensure that it is 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.

If the threads are not visible, determine the location of the system via ultrasound or other method. If the system is in the uterine cavity, it may be removed using narrow forceps. This may require dilatation of the cervical canal or other surgical intervention.

If the user wishes to continue using the same method, a new system can be inserted at the time of removal.

- 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.

4.3 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;
- Progestogen-dependent tumors;
- Undiagnosed abnormal uterine bleeding;
- Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity;
- Conditions associated with increased susceptibility to infections;
- Acute liver disease or liver tumor
- Hypersensitivity to the active substance or to any of the excipients.

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 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

Mirena may be used with caution in women who have congenital heart disease or valvular heart disease at risk of infective endocarditis.

Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of Mirena.

Irregular bleedings may mask some symptoms and signs of 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.

Due to the limited exposure in Mirena trials in the indication protection from endometrial hyperplasia during estrogen replacement therapy, the available data are not sufficient to confirm or refute a risk for breast cancer when Mirena is used in this indication.

1. Medical examination/consultation

Before insertion, the woman must be informed of the efficacy, risks 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 the insertion should be followed carefully. Insertion and removal may be associated with some pain and bleeding. The procedure may precipitate fainting as a vasovagal reaction, or a seizure in an epileptic patient.

The women 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.

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 case bleeding disturbances appear after commencing estrogen replacement therapy.

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

2. Infrequent bleeding/amenorrhea

In women of fertile age, infrequent bleeding and amenorrhea develop gradually in 57% and 16% of women during the first year of use, respectively. By the end of Year 8 of Mirena use, infrequent bleeding and amenorrhea 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.

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

3. Pelvic infection

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.

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.

4. 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. As Mirena decreases menstrual flow, increase of 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; the 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.

5. 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 some time later and may decrease the effectiveness of Mirena. Such a system must be removed.

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 2). 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 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 (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=41910 insertions)

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

6. 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 1 year, the ectopic pregnancy rate with Mirena was 0.02%. 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 ectopic pregnancy is increased.

7. 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.

8. 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. Ovarian cysts have been reported as adverse drug reactions in approximately 7% of women using Mirena. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

In most cases, the ovarian cysts disappear spontaneously during two to three months' observation. Should this not happen, continued ultrasound monitoring and other diagnostic/therapeutic measures are recommended. Rarely, surgical intervention may be required.

4.5 Interaction with other medicinal products and other forms of interaction

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 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 Pregnancy and lactation

- Pregnancy

The use of Mirena during an existing or suspected pregnancy is contraindicated (see section 'Contraindications').

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 labor. 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.

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

- Lactation

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 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.

- Fertility

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

4.7 Effects on ability to drive or use machines

Not known.

4.8 Undesirable effects

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

Tabulated list of adverse reactions

The frequencies of adverse drug reactions (ADRs) reported with Mirena are summarized in table 3 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 12,101woman-years.

Adverse reactions in clinical trials in the indication protection from 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 3: adverse drug reactions

System Organ Class	Very Common	Common	Uncommon	Rare	Unknown
Immune system disorders					Hypersensitivity including rash, urticaria and angioedema
Psychiatric disorders		Depressed mood/ Depression			
Nervous system disorders	Headache	Migraine			
Gastrointestinal disorders	Abdominal/pelvic pain	Nausea			
Skin and subcutaneous tissue disorders		Acne Hirsutism	Alopecia		
Musculosceletal, 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 Dysmenorrhea 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 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 'Special warnings and precautions for use'). 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.

Description of selected adverse reactions

When a woman becomes pregnant with Mirena in situ, the relative risk of ectopic pregnancy is increased.

The removal threads may be felt by the partner during intercourse.
The risk of breast cancer is unknown when Mirena is used in the indication protection from endometrial hyperplasia during estrogen replacement therapy. Cases of breast cancer have been reported (frequency unknown, see section 'Special warnings and precautions of use').

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.

Cases of sepsis (including group A streptococcal sepsis) have been reported following IUD insertion (see section 'special warnings and precautions for use').

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-estrogenic activity used in gynecology 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 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 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 fertilization. Ovulation is inhibited in some women.

The contraceptive efficacy of Mirena up to 5 years has been studied in 5 major clinical studies with 3330 women using Mirena. The contraceptive efficacy during extended use beyond 5 years has been studied in the Mirena Extension trial with 362 women using Mirena.

The contraceptive efficacy of Mirena is summarized in the table below.

Table 4: Contraceptive efficacy

Contraceptive Efficacy within the first 5 years (N= 3330, Pooled data of contraceptive trials up to 5 Years)	
Year 1 Pearl Index	0.2
Years 1-5 cumulative failure rate (%)*	**0.7**
Contraceptive Efficacy beyond 5 years (N=362, Mirena Extension Trial)	
Year 6 Pearl Index	0.34
Year 7 Pearl Index	0.40
Year 8 Pearl Index	0.00
Years 6-8 cumulative failure rate (%)*	**0.68**

*Kaplan-Meier estimate

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. In a large prospective comparative non-interventional cohort study with an observation period of 1 year including more than 43,000 Mirena users, the Pearl Index of Mirena was 0.06 (95% CI: 0.04-0.09). 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 the future fertility. About 80 % of the 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 the 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 oligomenorrhea or amenorrhea. 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 dysmenorrhea.

The efficacy of Mirena in preventing endometrial hyperplasia during continuous estrogen treatment has been equally good when administering estrogen either orally or transdermally. The observed hyperplasia rate under estrogen 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 5.

Table 5: Estimated in vivo release rates for Mirena:

Time	Estimated *in vivo* release rate [µg/day]
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 1st year	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. 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 6:

Table 6: 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 pg/ml (25th to 75th 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 estrogen treatment, the serum levonorgestrel concentration at 12

months is increased to approx. 478 pg/ml (25th to 75th percentiles: 341 pg/ml to 655 pg/ml) due to the induction of SHBG by oral estrogen 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 concentration) of the total levonorgestrel concentration in serum. The concentration of SHBG declined on average by about 20% during the first two months after insertion of Mirena and 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.

Biotransformation
Levonorgestrel is extensively metabolized. The most important metabolic pathways are the reduction of the Δ4-3-oxo group and hydroxylations at position 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 feces 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 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

The preclinical safety evaluation 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. 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 have not revealed bio-incompatibility.

6. PHARMACEUTICAL PARTICULARS

List of excipients
Polydimethylsiloxane elastomer
Silica, colloidal anhydrous
Polyethylene
Barium sulphate
Iron oxide

Incompatibilities
Not applicable.

Shelf Life
Please refer to labels.

Special precaution for storage
Store below 30°C.

Nature and contents of container
Carton containing one sterile system.

Instructions for use/handling
See “Insertion Instructions”.

Manufacturer
Bayer Oy
Turku, Finland

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2 May 2023