Mirena prescribing information

This provides medical and scientific information on Mirena in general. Please refer to the local Summary of Product Characteristics for the information applicable in your country.
1. NAME OF THE MEDICINAL PRODUCT
Mirena 20 micrograms/24 hours intrauterine delivery system

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Levonorgestrel 52 mg. The initial release rate is 20 micrograms /24 hours. 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 T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Removal threads are attached to the loop. The 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

   Protection from endometrial hyperplasia during estrogen replacement therapy

4.2 Dosage and method of administration
4.2.1 Method of administration
Mirena is inserted into the uterine cavity and is effective for five years.
The in vivo dissolution rate is approximately 20 µg/24 hours initially and is reduced to 10 µg/24 hours after five years. The mean dissolution rate of levonorgestrel is about 14 µg/24 hours over the time up to five years.

In women under hormonal replacement therapy, Mirena can be used in combination with oral or transdermal estrogen preparations without progestogens.
Mirena, when inserted according to the insertion instructions, has a failure rate of approximately 0.2% at 1 year and a cumulative failure rate of approximately 0.7% at 5 years.
• Insertion and removal/replacement

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, physical examination and ultrasound should be performed immediately to exclude perforation.

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.

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

If pregnancy is not desired, the removal should be carried out during the menstruation in women of fertile age, provided that there appears to be a menstrual cycle. If the system is removed in the midcycle and the woman has had intercourse within a week, she is at a risk of pregnancy unless a new system is inserted immediately following removal.

After removal of Mirena, the system should be checked to be intact. During difficult removals, single cases have been reported of the hormone cylinder sliding over the horizontal arms and hiding them together inside the cylinder. This situation does not require further intervention once completeness of the IUS has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

• 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 Children and adolescents

Safety and efficacy of Mirena have been established in women of reproductive age. 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 “Contraindications”).

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;
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 of 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. Antibiotic prophylaxis should be administered to these patients when inserting or removing the IUS.

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.

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 young nulligravid women, nor for postmenopausal women with advanced uterine atrophy.

Available data shows that Mirena does not increase the risk for breast cancer in pre-menopausal women under 50 years of age. 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.

**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, examination of the breasts, and a cervical smear should be performed. 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. Because the insertion technique 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 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.

**Oligo/amenorrhea**

In women of fertile age, oligomenorrhea and amenorrhea develop gradually in 57% and 16% of women, 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.

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

The insertion tube helps to prevent Mirena from contamination with micro-organisms during the insertion and the Mirena inserter has been designed to minimize the risk of infections. In users of copper intrauterine devices, the highest rate of pelvic infections occurs during the first month after insertion and decreases later. Some studies suggest that the rate of pelvic infection in users of Mirena is lower than with copper-releasing intrauterine devices. 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.

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

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.

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 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), 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 the insertion up to 36 weeks after giving birth were associated with an increased risk of perforation (see Table 1). These risk factors were independent of the type of IUD inserted.

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

<table>
<thead>
<tr>
<th>Insertion ≤ 36 weeks after delivery</th>
<th>Breastfeeding at time of insertion</th>
<th>Not breastfeeding at time of insertion</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6 (95% CI 3.9-7.9; n=6047 insertions)</td>
<td>1.7 (95% CI 0.8-3.1; n=5927 insertions)</td>
<td></td>
</tr>
<tr>
<td>Insertion &gt; 36 weeks after delivery</td>
<td>1.6 (95% CI 0.0-9.1; n=608 insertions)</td>
<td>0.7 (95% CI 0.5-1.1; n=41910 insertions)</td>
</tr>
</tbody>
</table>

The risk of perforation may be increased in women with fixed retroverted uterus.
**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%. his rate is lower than in women not using any contraception (0.3-0.5% per year). The absolute risk of ectopic pregnancy in Mirena users is low. However, when a woman becomes pregnant with Mirena in situ, the relative likelihood of ectopic pregnancy is increased.

**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.

**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 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**

The metabolism of progestagens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). 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.

**4.6 Pregnancy and lactation**

**4.6.1 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. If the intrauterine contraceptive cannot be gently removed, termination of the pregnancy may be considered. If the woman wishes to continue the pregnancy and the 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. Ectopic pregnancy should be excluded. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever. Because of the intrauterine administration and the local exposure to the hormone, the possible occurrence of virilizing effects in the fetus 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

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. 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.

4.7 Effects on ability to drive or use machines

Not known.

4.8 Undesirable effects

< For US see Appendix I>

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, 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.

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

4.8.2 Tabulated list of adverse reactions

The frequencies of adverse drug reactions (ADRs) reported with Mirena are summarized in the table below. Frequencies are defined as very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥ 1/1000 to <1/1000), rare (≥1/10000 to <1/10000) 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 estrogen replacement therapy (including 514 women and 1218.9 woman-years) were observed at a similar frequency unless specified by footnotes.
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 clinical trials that excluded breastfeeding women. In a large prospective comparative non-interventional cohort study in IUD users, the frequency of perforation in women who were breastfeeding or had an insertion up to 36 weeks after delivery was “uncommon” (see section “Special warning and precautions for use”).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity including rash, urticaria and angioedema</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>Depressed mood/ Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td></td>
<td>Migraine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal/pelvic pain</td>
<td></td>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td>Acne Hirsutism</td>
<td>Alopecia</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td></td>
<td></td>
<td>Back pain**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorrhoea and amenorrhoea Vulvovaginitis* Genital discharge*</td>
<td></td>
<td>Upper genital tract infection Ovarian cyst Dysmenorrhoea Breast pain** Intra-uterine contraceptive device expelled (complete and partial)</td>
<td>Uterine perforation</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td>Blood pressure increased</td>
<td></td>
</tr>
</tbody>
</table>

**Endometrial protection trials: “very common”

*** This frequency is based on clinical trials that excluded breastfeeding women. In a large prospective comparative non-interventional cohort study in IUD users, the frequency of perforation in women who were breastfeeding or had an insertion up to 36 weeks after delivery was “uncommon” (see section “Special warning and precautions for use”).
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.

Reproductive system disorders:
The removal threads may be felt by the partner during intercourse.

Breast disorders:
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 special precautions of use”).

Injury, poisoning and procedural complications:
The following ADRs have been reported in connection with the insertion or removal procedure of Mirena:
Procedural pain, procedural bleeding, insertion-related vasovagal reaction with dizziness or syncope. The procedure may precipitate a seizure in an epileptic patient.

Infections and Infestations:
Cases of sepsis (including group A streptococcal sepsis) have been reported following IUD insertion (see section 4.4 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 has been studied in 5 major clinical studies with 3330 women using Mirena. The failure rate (Pearl Index) was approximately 0.2% at 1 year and the cumulative failure rate was approximately 0.7% at 5 years. The failure rate also includes pregnancies due to undetected expulsions and perforations. Similar contraceptive efficacy has been observed in a large post-marketing study with more than 17000 women using Mirena. 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 amenorrhoic.

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.

**Pharmacokinetic properties**

The active ingredient of Mirena is levonorgestrel. Levonorgestrel is directly released into the uterine cavity. The in vivo release rate of levonorgestrel is initially approximately 20 μg/24 hours and declines to 10 μg/24 hours after 5 years.

**Absorption**

Following insertion, levonorgestrel is released into the uterine cavity without delay based on serum concentration measurements. The high local drug exposure in the uterine cavity leads to a strong concentration gradient via the endometrium to the myometrium (gradient endometrium to myometrium >100-fold), and to low concentrations of levonorgestrel in serum (gradient endometrium to serum>1000-fold).
Distribution
Levonorgestrel is bound non-specifically to serum albumin and specifically to SHBG. About 1-2% of the circulating levonorgestrel is present as free steroid and 42-62% is specifically bound to SHBG. During the use of Mirena, the concentration of SHBG declines. Accordingly, the fraction bound to SHBG decreases during the treatment and the free fraction increases. The mean apparent volume of distribution of levonorgestrel is about 106 L.

After insertion of Mirena, levonorgestrel is detectable in serum after 1 hour. The maximum concentration is reached within 2 weeks after insertion. In correspondence with the declining release rate, the median serum concentration of levonorgestrel declines from 206 pg/ml (25th to 75th 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.

Body weight and serum SHBG concentration have been shown to affect systemic levonorgestrel concentration i.e. low body weight and/or a high SHBG level increase levonorgestrel concentration. In women of reproductive age with a low body weight (37 to 55 kg) the median serum concentration of levonorgestrel is about 1.5-fold higher.

In postmenopausal women using Mirena together with non-oral 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.

Biotransformation
Levonorgestrel is extensively metabolized. The major metabolites in the plasma are the unconjugated and conjugated forms of 3α,5β-tetrahydrolevonorgestrel. Based on in vitro and in vivo studies, CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel, CYP2E1, CYP2C19 and CYP2C9 may also be involved, but to a smaller extent.

Elimination
The total clearance of levonorgestrel from plasma is approximately 1.0 ml/min/kg. Only trace amounts of levonorgestrel are excreted in unchanged form. The metabolites are excreted with the 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. During use of Mirena a mean SHBG decrease of about 30% was observed, which leads to a decrease of levonorgestrel in serum indicating non-linear pharmacokinetics of levonorgestrel with regard to time. Based on the mainly local action of Mirena, no impact on the efficacy of Mirena is expected.

5.3 Preclinical safety data
The preclinical safety evaluation revealed no special hazard for humans based on studies of safety pharmacology, toxicity, genotoxicity, and carcinogenic potential of levonorgestrel. Levonorgestrel is a well-established progestogen. The safety profile following systemic administration is well documented. A study in monkeys with intrauterine delivery of levonorgestrel for 12 months confirmed local pharmacological activity with good local tolerance and no signs of systemic toxicity. No embryotoxicity was seen in the rabbit following intrauterine administration of levonorgestrel. The 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, guinea pigs, rabbits and in vitro test systems have not revealed bioincompatibility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polydimethylsiloxane elastomer
Silica, colloidal anhydrous
Polyethylene
Barium sulphate
Iron oxide