1. NAME OF MEDICINAL PRODUCT
Mirena 20 micrograms/24 hours intrauterine delivery system

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Levonorgestrel 52mg. The initial release rate is 20 micrograms/24hours.
For a full list of excipients, see section 6.1, '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 Indications
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 and is effective for five years in the indications for contraception and idiopathic menorrhagia.

In the indication for the protection from endometrial hyperplasia during oestrogen replacement therapy, clinical data beyond 4 years of use are limited. Mirena should therefore be removed after 4 years.

The in *vivo* dissolution rate is approximately 20 μg/24 hours initially and is reduced to approximately 18 μg/24 hours after 1 year and to 10 μg/24hours after 5 years. The mean dissolution rate of levonorgestrel is about 15 μg/24hours 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. It can be replaced by a new system at any time of the cycle.

Mirena can also be inserted immediately after the 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 oestrogen replacement therapy, Mirena can be inserted at any time in an amenorrhoeic 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 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.

The system should be removed after five years in the indications for contraception and menorrhagia and after 4 years for endometrial protection. 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, 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 risk of pregnancy. To ensure continuous contraception a new system should be immediately inserted or an alternative contraceptive method should have been initiated.

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.

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

4.2.2 Additional information on special populations

4.2.2.1 Pediatrics

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 tumour (see section 4.3, '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 tumours;
- Undiagnosed abnormal uterine bleeding;
- Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity;
- Conditions associated with increased susceptibility to infections;
- Past attack of bacterial endocarditis or of severe pelvic infection in a woman with an anatomical lesion of the heart or after any prosthetic valve replacement;
- Active or previous severe arterial disease, such as stroke or myocardial infarction;

- Liver tumour or other acute or severe liver disease;

- Acute malignancies affecting the blood or leukaemias except when in remission;
- Recent trophoblastic disease while hCG levels remain elevated;
- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warning and special 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, crescendo migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischaemia
- unusually frequent or exceptionally severe headache
-jaundice
-marked increase in blood pressure
-malignancies affecting the blood or leukaemias in remission
-use of chronic corticosteroid therapy
-past history of symptomatic functional ovarian cysts
-severe arterial disease such as stroke or myocardial infarction
-thrombotic arterial or any current embolic disease
-Venous thromboembolism.

In general, women using hormonal contraception should be encouraged to give up smoking.

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. 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 postmenopausal women with advanced uterine atrophy.

Two observational studies have not provided evidence of an increased risk of breast cancer during the use of Mirena. Due to confounding factors 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 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. In the event of early signs of a vasovagal attack, insertion may need to be abandoned or the system removed.

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/or amenorrhea develops gradually in 57% and 16% of women during first year of use, 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 amenorrhoeic subjects unless indicated by other symptoms.

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:
Known risk factors for pelvic inflammatory disease are multiple sexual partners, frequent intercourse and young age. Pelvic infection may have serious consequences as 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.

Expulsion:

Symptoms of the partial or complete expulsion of any IUS may include bleeding or pain. However, a system can be expelled from the uterine cavity without the woman noticing it leading to loss of contraceptive protection. As the system 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 women 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.

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. This may be associated with severe pain and continued bleeding. If perforation is suspected the system should be removed as soon as possible.

In a large prospective comparative non-interventional cohort study in IUD users (N = 61,448 women) With a 1-year observational period, the incidence of perforation was 1.3 (95% CI:1.1 - 1.6) per 1000 insertions in the entire study cohort; 1.4 (95% CI: 1.1 - 1.8) per 1000 insertions in the Mirena cohort and 1.1 (95% CI: 0.7 - 1.6) per 1000 insertions in the copper IUD cohort. Extending the observational period to 5 years in a subgroup of this study (N=39,009 women using Mirena or copper IUD), the incidence of perforation detected at any time during the entire 5-year period was 2.0 (95% CI: 1.6-2.5) per 1000 insertions.

The study showed that both breastfeeding at the time of insertion and insertion up to 36 weeks after giving birth were associated with an increased risk of perforation (see Table 1). These risk factors were confirmed in the subgroup followed up for 5 years. Both risk factors were independent of the type of IUD inserted.

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

	Breastfeeding at time of insertion	Not breastfeeding at time of insertion
Insertion ≤ 36 weeks after delivery	5.6 (95% CI 3.9-7.9; n=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 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 a further 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 amenorrhoeic 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%. This rate is lower than in women not using any contraception (0.3-0.5% per year). The corresponding figure for the copper IUD is 0.12 per 100 woman years. 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 examination - first exclude pregnancy. 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 cystsdisappear 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

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

4.5.1 Effects of other medicinal products on Mirena
Interactions can occur with drugs that induce or inhibit microsomal enzymes, which can result in increased or decreased clearance of sex hormones.

Substances increasing the clearance of levonogestrel, e.g.:

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, rifabutin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St. John's wort.

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

Substances with variable effects on the clearance of levonorgestrel:
When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestin.

Substances decreasing the clearance of levonorgestrel (enzyme inhibitors) e.g.:
Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestin.

4.6 Pregnancy and lactation

4.6.1 Women of child-bearing potential/Contraception
4.6.2 Pregnancy
The use of Mirena during an existing or suspected pregnancy is contraindicated (see section 4.3, 'Contraindication'). 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 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. 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.

4.6.3 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 effects on infant growth or development when using Mirena after six weeks postpartum. Progestogen-only methods do not appear to affect the quantity or quality of breast milk. Uterine bleeding has rarely been reported in women using Mirena during lactation.

4.6.4 Fertility
The use of Mirena does not alter the course of future fertility. About 80% of the women wishing to become pregnant conceived within 12 months following the removal of Mirena.

4.7 Effects on ability to drive and use machines
Not known.

4.8 Undesirable effects

4.8.1 Summary of the safety profile
The majority of women experience changes in menstrual bleeding pattern after insertion of Mirena. During the first 90 days, prolonged bleeding is experienced by 22% and irregular bleeding by 67% of women after post-menstrual insertion of Mirena, decreasing 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 16% and 57% at the end of the first year of use, respectively.

When used in combination with oestrogen replacement therapy, most peri- and postmenopausal users of Mirena experienced spotting and irregular bleeding during the first months of the treatment. Thereafter bleeding and spotting decreased and about 40% of the users became totally free of bleeding during the last three months of the first year of treatment. Bleeding disturbances were more frequent in perimenopausal women when compared with postmenopausal women.

4.8.2 Tabulated list of adverse reactions
The frequencies of adverse drug reactions (ADRs) reported with Mirena are summarised in the table below. The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are are crude incidences of the events observed in clinical trials in the indications contraception and idiopathic menorrhagia/heavy menstrual bleeding, including 5091 women and 13320 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.

Table 2: adverse drug reactions

System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10000 to <1/1000)**	**Unknown**
Immune system					Hypersensitivity

disorders					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		
Musculoskeletal, connective tissue and bone disorders		Back pain**			
Reproductive system and breast disorders	Bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorrhoea and amenorrhoea. Vulvovaginitis* Genital discharge*	Upper genital tract infection Ovarian cyst 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".

4.8.3 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.

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 “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 Special warnings and precautions for use).

4.9 Overdose
Not applicable

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G02BA03

Levonorgestrel is a progestogen with anti-estrogenic activity used in gynaecology in various ways: as the progestogen component in oral contraceptives, in hormonal replacement therapy or alone for contraception in minipills 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 anti-proliferative 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 amenorrhoeic.

Mirena may be particularly useful for contraception in patients with excessive menstrual bleeding, and can be successfully used in the treatment of idiopathic menorrhagia. The volume of menstrual bleeding was decreased by about 88% in menorrhagic women by the end of three months of use. Menorrhagia caused by submucosal fibroids may respond less favourably. Reduced bleeding promotes the increase in the concentration of blood haemoglobin. Mirena also alleviates dysmenorrhea. .

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The efficacy of Mirena in preventing endometrial hyperplasia during continuous oestrogen treatment is the same when oestrogen is administered orally or transdermally. The observed hyperplasia rate under oestrogen therapy alone is as high as 20%. In clinical studies with a total of 634 perimenopausal and postmenopausal users of Mirena, no endometrial hyperplasia were reported in the postmenopausal group during the observation period up to 5 years.

5.2 Pharmacokinetic properties

The active ingredient of Mirena is levonorgestrel. Levonorgestrel is directly released into the uterine cavity.

Absorption

Following insertion Mirena releases levonorgestrel without delay. The in vivo release rate of levonorgestrel in the uterine cavity is initially approximately 20 µg/24 hours and declines to 10 µg/24 hours after 5 years.

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.

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. Levonogestrel binds with high affinity to SHBG. Accordingly, changes in the concentration of SHBG in serum result in an increase (at higher SHBG concentrations) or in a decrease (at lower SHBG concentrations) of the total levonorgestrel concentration in serum. The concentration of SHBG declined on average by about 20-30% during the first month after insertion of Mirena, remained stable during the first year and increased slightly thereafter. 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. 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.

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 with anti-oestrogenic

activity. The safety profile following systemic administration is well documented. Studies 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 have not revealed bio-incompatibility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Polydimethylsiloxane elastomer, Silica, colloidal anhydrous, polyethylene, barium sulphate, iron oxide

6.2 Incompatibilities
None known

6.3 Shelf-life
Please refer to labels

6.4 Special precautions for storage
Not applicable.

6.5 Nature and contents of container
The product is individually packed into a thermoformed blister package with a peelable lid.

6.6 Instructions for use and handling
As the insertion technique is different from intrauterine devices, special emphasis should be given to training in the correct insertion technique. Special instructions for insertion are in the package.

Mirena is supplied in a sterile pack which should not be opened until required for insertion. Each system should be handled with aseptic precautions. If the seal of the sterile envelope is broken, the system inside should be disposed of in accordance with the local guidelines for the handling of biohazardous waste. Likewise, a removed Mirena and inserter should be disposed of in this manner. The outer carton package and the inner blister package can be handled as household waste.

7. Manufacturer
Bayer Oy, Finland
Pansiontie 47 (P.O. Box 415)
20210 Turku Finland

8. Date of Revision of the Text
14 December 2021

If you would like to report a side effect for any Bayer Pharmaceutical or Consumer Health product, you can do it easily using our online reporting portal: https://safetrack-public.bayer.com/ or scan the QR code available below. Please also remember to seek medical advice directly from your doctor or pharmacist.

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