SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

MIRENA

52 mg levonorgestrel.

Intrauterine delivery systems

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Levonorgestrel 52 mg. The initial release rate is 20 µg per 24 hours.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Intrauterine delivery system (IUS)

The levonorgestrel (LNG) intrauterine delivery system consists of a white or almost white drug core covered with an opaque membrane, which is mounted on the vertical stem of a T-body. The T-body has a loop at one end of the vertical stem and two horizontal arms at the other end.
Brown removal threads are attached to the loop. The T-frame of MIRENA contains barium sulphate, which makes it visible in X-ray examination. The vertical stem of the intrauterine delivery system is loaded in the insertion tube at the tip of the inserter. The intrauterine delivery system and inserter are essentially free of visible impurities.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

One unit is inserted into the uterine cavity. One administration is effective for five years.
The *in vivo* dissolution rate is about 20 µg/ 24 hours initially and is reduced to approximately 18 µg/ 24 hours after 1 year and to 10 µg/ 24 hours after five years. The mean dissolution rate of levonorgestrel is about 15 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 oestrogen preparations without progestogens.

MIRENA, when inserted according to the insertion instructions, has a failure rate of approximately 0,2 % at 1 year and accumulative failure rate of approximately 0,7 % at 5 years. The failure rate may increase in case of expulsion or perforation.

Method of administration

Instructions for use/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. Special instructions for insertion are in the package.

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/replacement:

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. For timing of insertion to exclude pregnancy see "section 4.2".

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 maximise efficacy. Therefore, the instructions for the insertion should be followed carefully.

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

In women of fertile age MIRENA is to be inserted into the uterine cavity within seven days of the onset of menstruation. In this case no back up contraception is needed. MIRENA can be inserted at any time during the cycle if the physician can be reasonably certain (as defined by the World Health Organisation) that the woman is not pregnant. If insertion is more than seven days since menstrual bleeding started, a barrier method of contraception should be used, or the patient should abstain from vaginal intercourse for the next seven days to prevent pregnancy. Consider the possibility of ovulation and conception before using this product. Mirena is not suitable for use as post-coital contraceptive (see "section 4.4.")

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 insertion should be delayed until the uterus is involuted, however not earlier than six weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks

postpartum. It is recommended that MIRENA should only be inserted by medical practitioners/ healthcare professionals who are experienced in MIRENA insertion and/ or have undergone sufficient training for MIRENA insertion. 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.

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

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. If dilation is required, consider using analgesics and/or a paracervical block.

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 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 MIRENA has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

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 woman.

Insertion instructions:

See separate enclosed insertion instruction leaflet.

Important:
Should you suspect that the system is not in the correct position, remove it and insert a new one.

Removal of MIRENA:

MIRENA can be removed by pulling the removal 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. Unless a pregnancy is desired, the system should not be removed after the fifth day of the menstrual cycle in a sexually active woman.

Special populations

Geriatric patients:

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

Patients with renal impairment:

MIRENA has not been studied in women with renal impairment

Patients with hepatic impairment:

MIRENA is contraindicated in women with acute liver disease or liver tumour (see "section 4.3").

Paediatric population

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Known or suspected pregnancy (see "section 4.6");
Current or recurrent pelvic inflammatory disease;
Lower genital tract infection;
Postpartum endometritis;
Septic (infected) abortion during the past three months;
Cervicitis;
Cervical dysplasia;
Uterine or cervical malignancy;
Undiagnosed abnormal uterine bleeding;
Progestogen-dependent tumours;
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 tumour.

4.4 Special warning and precautions for use

MIRENA should be used with caution and only after specialist consultation; alternatively, 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 ischaemia;
- severe headache;
- jaundice;
- marked increase of blood pressure;
- severe arterial disease such as stroke or myocardial infarction.

There is no consensus about the possible role of progestogens, as in MIRENA, in patients with varicose veins and superficial thrombophlebitis in the causation of venous thromboembolism.

MIRENA should 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.

The available data are not sufficient to confirm or refute a risk for breast cancer when MIRENA is used in the indication protection from endometrial hyperplasia during oestrogen replacement therapy.

Oligo/amenorrhoea:

In women of fertile age, oligomenorrhoea and amenorrhoea develops in 57 % and 16 % of women respectively. The possibility of pregnancy should be considered if menstruation does not occur within 6 weeks of the onset of previous menstruation. A repeated pregnancy test is not necessary in amenorrhoea subjects unless indicated by other signs of pregnancy.

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

Pelvic infection:

The insertion tube helps to reduce contamination of MIRENA with micro-organisms during the insertion. The highest rate of pelvic infections occurs during the first month after insertion and decreases later.

Severe infections or sepsis (including group A streptococcal sepsis) can occur following IUD insertion such as MIRENA,

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 MIRENA may include bleeding or pain. However, the system can be expelled from the uterine cavity without the woman noticing it leading to loss of contraceptive protection. As MIRENA decreases menstrual flow, increase of menstrual flow may be indicative of an expulsion.

Risk of expulsion in increased in

- Women with history of heavy menstrual bleeding
- Women with greater than normal BMI at the time of insertion; this 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 that pregnancy has been excluded.

Perforation:

Perforation or penetration of the uterine corpus or cervix by MIRENA may occur, most often during insertion, although it may not be detected until sometime later, and may decrease the effectiveness of MIRENA. If this occurs MIRENA must be removed.

In a large European prospective comparative non-interventional cohort study in IUD users (N = 61448 women), with a 1-year observational period, the incidence perforation was 1,3 (95 % CI: 1,1 to 1,6) per 1000 insertions.

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 to 2.5) per 1 000 insertions.

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.

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)

	Breastfeeeding at time of insertion	**Not breastfeeding at time of insertion**
Insertion ≤36 weeks after delivery	5,6 (95 % CI 3,9 to 7,9, n = 6047 insertions)	1,7 (95 % CI 0,8 to 3,1, n = 5927 insertions)
Insertion >36 weeks after delivery	1,6 (95 % CI 0,0 to 9,1, n = 608 insertions)	0,7 (95 % CI 0,5 to 1,1, n = 41 910 insertions)

The risk of perforations 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 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 to 0,5 % per year). 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 cysts are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

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

4.5 Interaction with other medicines and other forms of interaction

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 nonnucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestin.

Substances decreasing the clearance of levonorgestrel (enzyme inhibitors), e.g.:

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of MIRENA during an existing or suspected pregnancy is contraindicated (see "section 4.3"). If the woman becomes pregnant when using MIRENA, removal of the system is recommended since any intrauterine contraceptive left in situ may increase the risk of abortion and preterm labour. Removal of MIRENA or probing of the uterus may result in spontaneous abortion. If the intrauterine contraceptive cannot be gently removed, termination of 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.

There have been isolated cases of masculinization of the external genitalia of the female foetus following local exposure to levonorgestrel during pregnancy with MIRENA in place.

Breastfeeding

About 0.1 % levonorgestrel dose is transferred to the infant during breastfeeding. Progestogen-only methods do not appear to affect the quantity or quality of breast milk. Non-hormonal contraceptive methods/devices are the methods of choice during lactation. However, if progestogen only contraception is judged as appropriate for lactating women, MIRENA may be used. Uterine bleeding has been reported in women using MIRENA during lactation.

Fertility

Upon removal of MIRENA, women usually return to their normal fertility.

4.7 Effects on ability to drive and use machines

Not known

4.8 Undesirable effects

a) 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. Amenorrhoea increases from 0 % to 16 % and infrequent bleeding increases from 11 % to 57 % from the first 90 days until the end of the first year of use respectively.

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

Adverse events reported in clinical studies:

The adverse drug reaction frequencies were observed in the clinical trials in the indication contraception and idiopathic menorrhagia/ heavy menstrual bleeding, including 5091 women and 12,101 woman-years.

Adverse reactions in clinical trials in the indication protection from endometrial hyperplasia during oestrogen replacement therapy (including 514 women and 1218,9 woman-years) were observed at a similar frequency unless specified by footnotes.

System Organ Class	Very Common ≥1/ 10	Common ≥ 1/100, < 1/10	Uncommon ≥ 1/1000, < 1/100	Rare ≥ 1/10000, <1/1000	Unknown
Immune system disorder					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		
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, Dysmenorrhoea, breast pain**, Intra-uterine contraceptive device expelled (complete and partial)	Uterine perforation***		
Investigations				Blood pressure increased	
* Endometrial protection trials: "common"					
** Endometrial protection trials: "very common"					
*** The 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 inserion up to 36 weeks after giving birth are independednt risk factors for perforation (see "section 4.4.").					

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 oestrogen replacement therapy.
Cases of breast cancer have been reported (frequency unknown, see "section 4.4.").

Injury, poisoning and procedural complications:

The following adverse drug reactions 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 epileptic patients.

Infections and infestations:

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

e) Other special populations

Post marketing side effects:

The following adverse reactions have been identified during post approval use of MIRENA:
Immune system disorders: Hypersensitivity including rash, urticarial and angioedema
Investigations: Blood pressure increased

Infections and infestations: Cases of sepsis (including group A streptococcal sepsis) have been reported following IUD insertion (see "section 4.4"). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to exposure to the medicine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Alternatively, you can report to Bayer SafeTrack site (https://www.safetrack-public.bayer.com).

4.9 Overdose

Not relevant

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A. 34 Other
Pharmacotherapeutic group: Plastic IUD with progestogen
ATC code: G02B03

Levonorgestrel is a progestogen with anti-oestrogenic activity.

Levonorgestrel intrauterine system has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentrations in the endometrium down-regulate oestrogen and progesterone receptors, making the endometrium insensitive to the circulating oestradiol and a strong antiproliferative effect is seen. Morphological changes of the endometrium and a weak local foreign body reaction are observed during use of the levonorgestrel intrauterine system.

Thickening of the cervical mucous prevents passage of the sperm through the cervical canal. The local milieu of the uterus and of the ovarian tubes inhibits sperm mobility and function, preventing fertilisation. Ovulation is inhibited in some women.

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 below:

Time	Estimated *in vivo* release rate [µg/24 hours]
Initial	20
1 year after insertion	18
5 years after insertion	10
Average over 5 years	15

Absorption

Following insertion, the levonorgestrel intrauterine system (52 mg) releases levonorgestrel. The *in vivo* release rate of levonorgestrel in uterine cavity is initially approximately 20 µg/ 24 hours and declines to 10 µg/ 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 (25^{th} to 75^{th} percentiles: 151 pg/ml to 264 pg/ml) at 6 months to 194 pg/ml (146 pg/ml to 266 pg/ml) at 12 months, and to 131 pg/ml (113 pg/ml to 161 pg/ml) at 60 months in women of reproductive age weighing above 55 kg.

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 levonorgestrel intrauterine system together with non-oral oestrogen treatment, the median serum concentration of levonorgestrel declines from 257 pg/ml (25^{th} to 75^{th} percentiles: 186 pg/ml to 326 pg/ml) at 12 months to 149 pg/ml (122 pg/ml to 180 pg/ml) at 60 months. When levonorgestrel intrauterine system is used together with oral oestrogen

treatment, the serum levonorgestrel concentration at 12 months is increased to approx. 478 pg/ml (25^{th} to 75^{th} percentiles: 341 pg/ml to 655 pg/ml) due to the induction of the Sex hormone-binding globulin (SHBG) by oral oestrogen treatment.

Distribution:

Levonorgestrel is bound non-specifically to serum albumin and specifically to Sex Binding Human Globulin (SBHG). Less than 2 % of the circulating levonorgestrel is presented 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 concentration) or in a decrease (at lower SHBG concentrations) of total levonorgestrel concentration in serum. The concentration of SHBG declined on average by about 20 to 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 litres.

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 metabolised. The most important metabolic pathways are the reduction of the Δ4-3-oxo group and hydroxylations at positions 2α, 1β and 16β, followed by conjugation. CYP3A4 is the main enzyme involved in the oxidative metabolism of LNG. The available *in vitro* data suggest that CYP mediated biotransformation reactions may be of minor relevance for levonorgestrel compared to reduction and conjugation.

Elimination

The total clearance of levonorgestrel from plasma is approximately 1.0 ml/min/kg. Only trace amounts of levonorgestrel are excreted in unchanged form. The metabolites are excreted with the faeces and urine at an excretion ratio of about 1. The excretion half-life, which is mainly represented by the metabolites, is about 1 day

Linearity/ non-linearity

The pharmacokinetics of levonorgestrel is dependent on the concentration of SHBG, which itself is influenced by oestrogens and androgens. A decrease of SHBG concentration leads to a decrease of total levonorgestrel concentration in serum indicating non-linear pharmacokinetics of levonorgestrel with regard to time. Based on the mainly local action of Mirena, no impact on the efficacy of Mirena is expected

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

6.1 List of excipients

Barium sulphate
Colloidal anhydrous
Iron oxide
Polydimethylsiloxane elastomer, silica
Polyethylene.
Other components
T-Body for LNG IUS 52 mg
Thread PE brown thin
Integrated administration device
Inserter for LNG IUS 52 mg

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C. Protect from moisture and direct sunlight.

6.5 Nature and contents of container

The system, with the accessories, is packed into a heat-sealed sterilisation pouch.

6.6 Special precautions for disposal and other handling of the product

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

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg No.: 1968/011192/ 07
27 Wrench Road
Isando
Telephone: 011 921 5911
Email: regulatory_southafrica@bayer.com

8. REGISTRATION NUMBER(S)

A 32/34/0332

9. DATE OF FIRST AUTHORISATION

26/02/1999

10. DATE OF REVISION OF THE TEXT

09 September 2025