SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM:

MIRENA Intrauterine delivery system

COMPOSITION:

Levonorgestrel intrauterine system 20 µg/ 24 hours. Each sterile intrauterine system contains levonorgestrel 52 mg.

PHARMACOLOGICAL CLASSIFICATION:

A. 34. Other.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Levonorgestrel is a progestogen.

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 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 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.

Pharmacokinetic properties

Following insertion of the Levonorgestrel intrauterine system (52 mg), the initial release of levonorgestrel into the uterine cavity is 20 µg/ 24 hours. This provides a stable plasma levonorgestrel concentration which, after the first weeks following insertion, levels off at 0,4 to 0,6 nmol/l (150 to 200 pg/ ml) in women of fertile age and about 1 nmol/ l (300 pg/ ml) in women receiving oestrogen replacement therapy. After long-term wearing periods of 12, 24 and 60 months in young women, levonorgestrel concentrations of 180 ± 66 pg/ ml, 192 ± 140 pg/ml and 159 ± 60 pg/ ml were observed in the plasma. In postmenopausal users of levonorgestrel intrauterine system (52 mg), plasma levonorgestrel concentrations have been 276 ± 119 pg/ ml, 196 ± 87 pg/ ml and 152 ± 43 pg/ ml, respectively.

The pharmacokinetics of levonorgestrel itself has been extensively studied and reported in the literature. Orally administered levonorgestrel is rapidly and completely absorbed and the absolute bioavailability is about 90 %. Levonorgestrel is bound to serum albumin and to sex hormone-binding globulin (SHBG). The relative distribution (free, albumin-bound, SHBG-bound) depends on the SHBG concentration in the serum. Only about 2, 5 % of the total serum drug levels are present as free steroid, but 47, 5 % and 50 % are bound to SHBG and albumin, respectively.

For levonorgestrel, a mean volume of distribution of approximately 137 litres and a metabolic clearance rate from serum of about 5, 7 litres/ hour were reported. A terminal half-life of levonorgestrel in serum in the range of about 14 to 20 hours can be observed after single dose administration. Levonorgestrel is

excreted as metabolites at about equal proportions with urine and faeces. The metabolites have only weak or no pharmacological activity. The principal metabolite in urine is tetrahydronorgestrel which accounts for approximately 10 % of the radioactivity recovered from the urine after administration of radiolabelled levonorgestrel.

About 0, 1 % of the maternal dose of levonorgestrel can be transferred via milk to the breastfed infant.

INDICATIONS

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

CONTRA-INDICATIONS

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;
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;
Hypersensitivity to the constituents of the preparation.

WARNINGS

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 ischaemia;
- exceptionally severe headache;
- jaundice;
- marked increase of blood pressure;
- severe arterial disease such as stroke or myocardial infarction.

In women using progestogen-only pills some recent epidemiological studies indicated that there may be a slightly increased risk of venous thromboembolism, but the results were statistically not significant. However, appropriate diagnostic and therapeutic measures should be undertaken immediately if there are symptoms or signs of thrombosis. Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; “acute” abdomen. Symptoms or signs indicating

retinal thrombosis are: unexplained partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions.

There is no consensus about the possible role of progestogens, such as in Mirena, in patients with varicose veins and superficial thrombophlebitis in the causation of venous thromboembolism.
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 women when inserting or removing the intrauterine delivery system.
Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of Mirena.

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

Mirena is not the method of first choice for young nulligravid women, nor for postmenopausal women with advanced uterine atrophy.

Oligo/amenorrhoea

In women of fertile age, oligomenorrhoea and/or amenorrhoea develops gradually in about 20 % of the users. 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 amenorrhoeic 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 prevent Mirena from contamination with micro-organisms during the insertion. The highest rate of pelvic infections occurs during the first month after insertion and decreases later. 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.

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. 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 Mirena may occur rarely, most often during insertion. The system must be removed. The risk of perforation may be increased in post-partum insertion (see section on Dosage and Direction for use), in lactating women, and 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. The rate of ectopic pregnancy in users of Mirena has been 0, 06 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 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 system may have been expelled. 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.

Delayed follicular atresia

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. Enlarged follicles have been diagnosed in about 12 % of the subjects using Mirena. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

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

INTERACTIONS

The metabolism of progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, and carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). The influence of these drugs on the contraceptive efficacy of Mirena is not known, but is not believed to be of major importance due to the local mechanism of action.

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PREGNANCY AND LACTATION

Pregnancy

Mirena is not to be used during an existing or suspected pregnancy. 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 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, teratogenicity (especially virilisation) cannot be excluded.

Lactation

Levonorgestrel has been identified in breast milk of women using Mirena.

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.

DOSAGE AND DIRECTIONS FOR USE

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 about 11 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 oestrogen preparations without progestogens.

Mirena, when inserted according to the insertion instructions, has a failure rate of approximately 0.1 % per year. The failure rate may increase in case of expulsion or perforation.

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.

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

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, 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 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. 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 physicians/ health care professionals who are experienced in Mirena insertion and/ or have undergone sufficient training for Mirena insertion. In case of a difficult insertion, physical examination and ultrasound should be performed immediately to exclude perforation.

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

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.

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. Otherwise contraception has to be ensured with other methods (e.g. condoms) starting at least 7 days before the removal. When the woman has no menses, she should also use barrier methods of contraception starting seven days before removal and has to continue with this until her menstruation reappears

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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Adverse effects are more common during the first months after insertion. In addition to the adverse effects listed under "Warnings" the following undesirable effects have been reported in users of Mirena, although a causal relationship with Mirena could not always be confirmed.
Very common side effects (occurring in more than 10 % of users) include uterine/ vaginal bleeding including spotting, oligomenorrhea, amenorrhea and benign ovarian cysts.

Different kinds of bleeding changes (frequent, prolonged or heavy bleeding, spotting, oligomenorrhoea, and amenorrhoea) are experienced by all users of Mirena. In fertile women the average number of spotting days/months decreases gradually from nine to four days during the first six months of use. The percentage of women with prolonged bleeding (more than eight days) decreased from 20 % to 3 % during the first three months of use. In clinical studies during the first year of use, 17 % of women experienced amenorrhoea of at least three months duration.

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 because 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.

The frequency of benign ovarian cysts depends on the diagnostic method used, and in clinical trials enlarged follicles have been diagnosed in 12 % of the subjects using Mirena. Most of the follicles are asymptomatic and disappear within three months.

The table below reports adverse reaction by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data.

System Organ Class	**Common** **> 1/100, < 1/10**	**Uncommon** **> 1/1000, < 1/100**	**Rare** **> 1/10000, < 1/1000**
Psychiatric disorders	Depressed mood, Nervousness, Decreased libido	Altered mood	
Nervous system disorders	Headache	Migraine	
Gastrointestinal disorders	Abdominal pain Nausea	Abdominal distention	
Skin and subcutaneous tissue disorders	Acne	Alopecia Hirsutism Pruritus Eczema	Rash Urticaria

Musculoskeletal, connective tissue and bone disorders	Back pain		
Reproductive system and breast disorders	Pelvic pain Dysmenorrhoea Vaginal discharge Vulvovaginitis Breast tenderness Breast pain Intra-uterine contraceptive device expelled	Pelvic inflammatory disease Endometritis Cervicitis/ Papanicolaou smear normal, class II	Uterine perforation
General disorders and administration site conditions		Oedema	
Investigations	Weight increase		

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

In addition, cases of breast cancer have been reported in Mirena users (frequency unknown)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Not relevant.

IDENTIFICATION

The levonorgestrel 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. Removal threads are attached to the loop. 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.

PRESENTATION

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

STORAGE INSTRUCTIONS

Store below 30°C. Protect from moisture and direct sunlight. Keep out of reach of children.

REGISTRATION NUMBER

32/34/0332

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DATE OF PUBLICATION OF THE PACKAGE INSERT

12 February 2009

CCDS date 0307/SA3.2/0408