

**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE
PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986**

The medicine is dispensed with a doctor's prescription only

Mirena[®]

Intrauterine Delivery System

The active ingredient is levonorgestrel 52 mg (20 micrograms/24 hours)

Inactive ingredients and allergens in the preparation – see section 6 'Further Information'.

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

1) WHAT IS THE MEDICINE INTENDED FOR?

What is Mirena?

Mirena is an intrauterine delivery system which releases at a steady rate the hormone levonorgestrel inside the womb after its installation.

The system is intended for treatment of the following conditions: for contraception, for treatment of heavy menstrual bleeding of unknown cause, and for protecting the endometrium as part of estrogen-containing hormone replacement therapy (HRT).

For contraception and for treatment of heavy menstrual bleeding, Mirena can be used for up to 5 years.

If you are using Mirena for protection of the endometrium during hormone replacement therapy, the Mirena system should be removed after 4 years. It is not known if Mirena is effective in protecting the endometrium as part of HRT beyond 4 years.

Therapeutic group: progestogens.

How does Mirena work?

When used as a contraceptive, the hormone in Mirena prevents pregnancy by:

- a) controlling the growth of the endometrium so that it is not thick enough to enable pregnancy,
- b) thickening the mucus in the cervix, thus creating an obstruction for entry of the sperm,
- c) preventing the release of eggs (ovulation) in some women.

There are also some effects on the endometrium caused by the T-shape of the Mirena system.

For treatment of heavy menstrual bleeding: The hormone in Mirena reduces menstrual bleeding by controlling the development of the endometrium, and as a result, it is thinner and there is less bleeding each month.

As part of hormone replacement therapy: Menopause is a gradual process which usually takes place between the ages 45-55. Although the process is natural, it is often accompanied by bothersome symptoms, such as hot flushes and night sweats. These symptoms are due to a gradual decline in the levels of female sex hormones (estrogen and

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progesterone) produced by the ovaries. Estrogens can be used to relieve the symptoms of menopause. However, taking estrogens alone increases the risk of abnormal growth or cancer of the endometrium. Taking progestogen, like the hormone in Mirena (levonorgestrel), as part of HRT, reduces this risk by protecting the endometrium.

2) BEFORE USING THE MEDICINE

Do not use the medicine if:

- you are sensitive (allergic) to the active ingredient or to any of the other ingredients contained in the medicinal product (see section 6 'Further Information'),
- you are pregnant or there is a chance that you are pregnant,
- you have or have had any type of cancer or suspected cancer including: blood cancer (leukemia) unless currently in remission, uterine cancer, cervical cancer and breast cancer,
- you are suffering from an existing or recurrent pelvic inflammatory disease,
- you have or have had inflammation of the neck of the womb (cervix),
- you have unusual or unpleasant vaginal discharge or vaginal itching, as these may indicate an infection,
- you have or have had in the past inflammation of the endometrium after delivery,
- you have or have had a uterine infection after delivery or after an abortion within the past 3 months,
- you have an increased tendency to contract infections (according to a doctor's diagnosis),
- you have or have had abnormal results of a Pap test (cervical smear test, aimed to check if there are changes in the cells of the cervix),
- you have undiagnosed vaginal bleeding,
- you have structural changes in the uterus or myomas (fibroids) which cause distortion of the uterine cavity,
- you have or have had in the past liver problems,
- you have or have had in the past trophoblastic disease (a group of diseases that develop after pregnancy from the placental tissue), according to a doctor's diagnosis.

Do not use Mirena as part of HRT if you have had a stroke, heart attack or other heart problems in the past.

Special warnings regarding use of the medicine:

- If you suffer from gynecological infections, treatment of such should be successfully completed before installation of Mirena.
- Mirena is not suitable for use as an emergency contraceptive.
- You may experience some pain or bleeding during the insertion.
- **Before installation of Mirena, tell the doctor** if you suffer from epilepsy. In rare cases, a seizure may occur during installation.
- After the installation, some women feel as if they are going to faint. This effect is normal. The doctor will instruct you to rest for a while.
- After installation of Mirena, you should receive a patient reminder card from your doctor for follow-up examinations. Bring this card with you to every scheduled appointment.

Mirena may not be suitable for all women. Consult your doctor if:

- you have or develop migraine with visual disturbances, unusually bad or unusually frequent headaches,
- you have yellowing of the skin or whites of the eyes (jaundice),
- you have high blood pressure,
- you have had blood cancer (including leukemia), which is now in remission,

- you are on long-term steroid therapy,
- you have had an ectopic pregnancy in the past,
- you have had ovarian cysts in the past,
- you are having Mirena fitted for contraception or for treatment of heavy menstrual bleeding and have had a stroke, heart attack in the past, or if you have other heart problems,
- you have arterial disease,
- you have a history of blood clots (thrombosis),
- you are diabetic, as Mirena may affect glucose tolerance.

You may still be able to use Mirena if you have or have had some of the above-mentioned conditions. Your doctor will advise you. It is very important that you tell the doctor or nurse if any of the conditions described above develop for the first time while you have Mirena in place.

Psychiatric disorders

Some women using hormonal contraceptives including Mirena have reported depression or depressed mood. Depression can be serious and may sometimes lead to suicidal thoughts. If you experience mood changes and depressive symptoms, contact your doctor for further medical advice as soon as possible.

You must **refer to your doctor or nurse immediately if you develop painful swelling in your legs, sudden chest pain or difficulty breathing**. These signs may indicate a blood clot. It is very important to treat a blood clot promptly.

You must **refer to your doctor immediately if you develop persistent lower abdominal pain, fever, pain during sexual intercourse or abnormal bleeding**. If you get severe pain or fever shortly after Mirena has been installed, you may have a severe infection which **must** be treated immediately.

Use of sanitary pads is recommended. If you use tampons or menstrual cups, you should change them with care so as not to accidentally pull the device threads. If you think you may have pulled Mirena out of place (see section 3 – 'How should you use the medicine? - How can I tell whether Mirena system is in its required place?'), avoid intercourse or use a barrier contraceptive (such as condoms), and contact your doctor.

Smoking

It is recommended to stop smoking when using or taking preparations that contain hormones such as in Mirena.

Young and adolescent girls

Mirena is not intended for young and adolescent girls before beginning their first menstrual cycle.

Tests and follow-up

- **Before installing Mirena, the doctor will carry out** a medical examination which will include a pelvic examination, in order to rule out pregnancy and sexually transmitted diseases, and additional examinations such as a breast examination.
- When Mirena is installed as part of hormone replacement therapy, the doctor will first assess the signs from which you suffer, to ensure that Mirena treatment is given only if the signs of menopause indeed harm your quality of life. This assessment should be done by the doctor at least once a year. You should also read the patient leaflet of the estrogen medicine you are taking together with Mirena, before starting HRT, since there are important risk factors you should consider, such as the risk of endometrial cancer, breast cancer and blood clots.

- The system should be checked 6 weeks after it is fitted. Your doctor may determine how often you should be checked and which types of check-ups are necessary in your particular case.
- If you received a patient reminder card from your doctor, bring it with you to every scheduled appointment.

Drug interactions

If you are taking or have taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or the pharmacist. The effect of hormonal contraceptives such as Mirena may be reduced by the use of medicines that increase the amounts of enzymes made by the liver. Especially inform the doctor or pharmacist if you are taking:

- medicines used to treat epilepsy
- antifungal medicines (e.g., griseofulvin, fluconazole, itraconazole, ketoconazole, voriconazole)
- certain antibiotics [rifampicin and macrolides (e.g., clarithromycin, erythromycin)]
- medicines used to treat HIV (AIDS) and hepatitis C virus infections, so-called protease inhibitors and non-nucleoside reverse transcriptase inhibitors
- certain sedatives (barbiturates)
- medicines to treat chest pain (angina) and/or high blood pressure
- products containing the plant ingredient St. John's Wort

Pregnancy, breastfeeding and fertility

Do not use Mirena if you are pregnant or if there is a chance you may be pregnant.

It is very rare for women to become pregnant with Mirena in place.

Missing a period is not necessarily a sign of pregnancy, as some women may not have periods at all while using Mirena. However, in order to exclude the possibility of pregnancy, you should consider a pregnancy test if you have not had a period for 6 weeks. If the result of the test is negative, there is no need to carry out another test, unless you have other signs indicative of pregnancy (e.g., nausea, tiredness or breast tenderness).

If you do become pregnant while using Mirena, contact your doctor immediately to have Mirena removed. The removal of the device may cause a miscarriage. However, if Mirena is left in place during pregnancy, not only is the risk of having a miscarriage higher, but also the risk of preterm labor. If Mirena cannot be removed, ectopic pregnancy should be ruled out and talk with your doctor about the benefits and risks of continuing the pregnancy. If the pregnancy is continued, you will be closely monitored during your pregnancy and you should contact your doctor right away if you experience abdominal cramps, abdominal pain or fever.

Mirena contains a hormone, called levonorgestrel, and there have been isolated reports regarding effects on the genitalia of female babies if exposed to intra-uterine devices containing levonorgestrel while in the womb.

Consult the doctor before breastfeeding in combination with Mirena.

Very low levels of the hormone in Mirena pass into the breast milk, but these levels are lower than with any other hormonal contraceptive method.

Studies have shown that the rate of pregnancies in one year, among women who stopped using Mirena to become pregnant, is similar to that among women who do not use contraceptives.

3) HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the instructions for use.

Insertion of Mirena should be performed by a trained doctor, after a gynecological examination. The doctor will explain the installation procedure to you, as well as the possible risks associated with Mirena use. If you have any concerns regarding the use of the system, consult the doctor.

When used for contraception or heavy menstrual bleeding:

Starting to use Mirena:

- Before Mirena is inserted, you must ensure that you are not pregnant.
- You should have Mirena inserted within 7 days from the start of your menstrual bleeding (your period). When Mirena is inserted on these days, it works right away and will prevent you getting pregnant.
- If you cannot have Mirena inserted within the 7 days from the start of your menstrual bleeding, or if your menstrual bleeding is irregular, then Mirena can be inserted on any other day. In this case, you must not have had sexual intercourse without contraception since your last menstrual bleeding, and you should have a negative pregnancy test. Also, Mirena may not work right away. Use a barrier method of contraception (such as condoms) if you have intercourse during the first 7 days after Mirena is inserted.
- Mirena is not suitable for use as an emergency contraceptive.
- The possibility of becoming pregnant is approximately 2 women in 1,000 in the first year. The possibility of becoming pregnant increases in cases where Mirena comes out by itself (see below, under 'What should I do if Mirena comes out by itself?') or in cases of a perforation in the uterine wall (see section 4 'Side Effects').
- Usually, the menstrual bleeding becomes lighter after 3 to 6 months of treatment.

Starting to use Mirena after giving birth:

- Mirena can be inserted after giving birth once the uterus has returned to its normal size. This means, not earlier than 6 weeks after delivery (see section 4 'Side effects – Severe pain and prolonged bleeding').
- See also 'Starting to use Mirena' above for what else you need to know about the timing of insertion.

Starting to use Mirena after an abortion:

- Mirena can be inserted immediately after an abortion if the pregnancy was less than 3 months along, provided there is no genital infection and you have not had a septic abortion within the last three months. Mirena will then work as soon as it is inserted.

Replacing Mirena:

- Mirena can be replaced with a new Mirena at any time of your menstrual cycle. Mirena will then work as soon as it is inserted.

Changing from contraceptive pills to Mirena:

If Mirena is inserted while you are taking contraceptive pills, then Mirena can be inserted at any time (also on days of the month when you do not take a pill). Continue taking your contraceptive pills until you finish your current treatment cycle.

For hormone replacement therapy (HRT):

- If you no longer have menstrual bleeding then Mirena can be inserted at any time. If you still have menstrual bleeding, Mirena should be inserted during the last days of bleeding. Remind your doctor that you have had Mirena inserted, especially if they were not the person who inserted the Mirena.
- Mirena will begin to protect the lining of your womb as soon as it is inserted.

How can I tell whether Mirena system is in its required place?

- Gently put a finger into your vagina and feel the two thin threads attached to the lower end of Mirena. The doctor will show you how to do this.
- **Avoid pulling the threads** because you may accidentally pull out Mirena.
- If you cannot feel the threads, contact your doctor as soon as possible and in the meantime, avoid intercourse or use a barrier contraceptive (such as condoms). The threads may have been drawn up into the womb or cervical canal. If the threads cannot be found even by your doctor, they may have broken off, or Mirena may have come out by itself, or in rare cases, Mirena may have perforated the wall of your womb (see section 4 'Side Effects'). It may be necessary for you to have an ultrasound scan or x-ray to locate Mirena.

Consult the doctor if you can feel the lower end of the system itself with your fingers and also if you or your partner feel pain or discomfort during sexual intercourse.

What should I do if Mirena comes out by itself?

The muscular contractions of the uterus during menstruation may sometimes push the device out of place or expel it. This is more likely to occur if you are overweight at the time the device is inserted or have a history of heavy periods. If the device is out of place, it may not work as intended and therefore, the risk of pregnancy increases. If the device is expelled, you are not protected against pregnancy anymore.

Possible symptoms of an expulsion are pain and abnormal bleeding, but Mirena may also be expelled without you noticing. As Mirena decreases menstrual flow, increase of menstrual flow may be indicative of an expulsion. It is recommended that you check for the threads with your finger, for example while taking a shower. See also the previous section, 'How can I tell whether Mirena system is in its required place?'. If you have signs indicative of expulsion of the device or you cannot feel the threads, you should use another contraceptive (such as condoms), and consult your doctor.

Tell your doctor if there are any unexpected changes in your menstrual bleeding.

How will Mirena affect your periods?

Mirena will affect your menstrual cycle.

For all uses: You may have lighter periods, more painful periods or spotting (light bleeding in between periods) or irregular bleeding during the first few months following installation. You may have prolonged or heavier bleeding or an increase in the frequency of bleeding, usually during the first 2 to 3 months, before reduced bleeding is achieved. Overall, it is expected that there will be fewer days of bleeding in each month and you might eventually have no periods at all. This is due to the effect of the hormone (levonorgestrel) on the endometrium.

If you have had Mirena fitted **for treatment of heavy menstrual bleeding** usually your periods become lighter after 3 to 6 months of treatment. If you do not have lighter periods after 3 to 6 months, alternative treatments should be considered.

It is very important that you refer to the doctor if you have had Mirena fitted **as part of HRT** and after a long time from the fitting you start to have bleeding problems. The doctor must check you to be sure there are no changes in your womb.

The doctor may ask you to monitor your bleeding pattern.

If you are interested in stopping use of Mirena

The doctor can remove Mirena at any time. If you do not want to become pregnant, the Mirena system should be removed during the first 7 days of your period. If you did not remove Mirena during the first 7 days of your period, you must use another contraceptive measure (e.g., condoms) during the 7 days before removal of Mirena; this is because having sexual intercourse during this week may lead to pregnancy after removal of Mirena.

If you want to become pregnant, your fertility level is expected to return to the normal level after Mirena is removed. Studies have shown that among women who stopped using Mirena (in order to become pregnant), the rate of pregnancies during a year is identical to that of women who did not use contraceptives.

In any case, do not stop using Mirena without consulting the doctor or pharmacist.

If you have further questions regarding use of Mirena, consult the doctor or pharmacist.

4) SIDE EFFECTS

As with any medicine, use of Mirena can cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them. Side effects attributed to Mirena are most common during the first months after it is fitted and decrease as time goes on.

Refer to the doctor immediately if you experience any of the following **serious side effects**:

- **Severe pain or fever developing shortly after insertion** may be a sign of a severe infection which **must** be treated immediately. In rare cases, very severe infection (sepsis) can occur.
- **Severe pain and prolonged bleeding** which might be a sign of damage or tear in the wall of the womb (perforation). Perforation is uncommon, but occurs most often during placement, although it may not be detected until sometime later. A Mirena which has become lodged outside the cavity of the womb is not effective in preventing pregnancy and must be removed as soon as possible. You may need to have surgery to have Mirena removed. The risk of perforation is increased in breastfeeding women and in women who had a delivery up to 36 weeks before insertion and may be increased in women with the uterus fixed and leaning backwards (fixed retroverted uterus). If you suspect you may have experienced a perforation, contact the doctor immediately and remind him that you have Mirena inserted, especially if he was not the person who inserted it.

Possible signs and symptoms of perforation may include:

- severe pain (like menstrual cramps) or more pain than expected
 - heavy bleeding (after insertion)
 - pain or bleeding which continues for more than a few weeks
 - sudden changes in your menstrual cycle
 - pain during sexual intercourse
 - you can no longer feel the system threads (see in section 3 'How can I tell whether Mirena system is in its required place?').
- **Lower abdominal pain, especially if you have a fever or have missed a period or have unexpected bleeding.** These might be signs of an ectopic pregnancy. The risk of ectopic pregnancy in Mirena users is low. However, when a woman becomes pregnant with Mirena in place, the likelihood of ectopic pregnancy is increased.
 - **Lower abdominal pain or pain and difficulty having sexual intercourse.** These may be signs of ovarian cysts or pelvic inflammation. It is important to rule out pelvic inflammation, as it can reduce your chances of becoming pregnant and increase the risk of ectopic pregnancy.

Other side effects

Very common side effects - effects that occur in more than 1 in 10 patients

- Vaginal bleeding including spotting
- Absent, light or irregular menstrual periods

Common side effects - effects that occur in less than 1 in 10 patients

- Ovarian cysts
- Menstrual pains
- Weight gain
- Depression, nervousness
- Headache
- Migraine
- Dizziness
- Abdominal, back or pelvic pain
- Nausea
- Acne
- Increased growth of hair on the face and body
- Reduced sex drive
- Increased vaginal discharge
- Inflammation of the vagina and vulva
- Tender and painful breasts
- Expulsion of the system

Uncommon side effects - effects that occur in less than 1 in 100 patients

- Perforation of the womb (see in section 4 'Serious side effects')
- Reproductive system infections that may cause: vaginal itching; pain on passing urine; lower abdominal pain due to inflammation of the womb, ovaries or fallopian tubes
- Infection or inflammation of the endometrium, which may cause a sharp, foul-smelling vaginal discharge (endometritis)
- Inflammation of the cervix
- Swelling of the abdomen, legs or ankles
- Hair loss
- Itchy skin including eczema
- Skin discoloration/increased skin pigment especially on the face (chloasma)

Rare side effects - effects that occur in less than 1 in 1,000 patients

- Rashes

Side effects of unknown frequency (effects whose frequency has not yet been determined)

- Sensitivity reactions (allergy) including signs such as: rash, itching or sudden swelling of the face, mouth, tongue and/or throat
- Increased blood pressure

Your partner may feel the Mirena removal threads during sexual intercourse.

Every woman is at risk of breast cancer, but it is rare in women under the age of 40. Breast cancer has been reported in Mirena users, although the risk rate and frequency are unknown.

In pre-menopausal women, the frequency of breast cancer among women who used Mirena is possibly similar to the frequency associated with using combined contraceptives (containing estrogen and progesterone hormones), but the evidence for this is less conclusive.

In women who no longer menstruate (post-menopause), use of HRT slightly increases the risk of breast cancer. Although the risk of developing breast cancer is higher with combined estrogen and progestogen HRT than with estrogen-only HRT, the risk of developing breast cancer when Mirena is used as a progestogen replacement is not yet known. It is important to read the patient leaflet of the estrogen medicine you are using, for further information. It is particularly important to regularly check your breasts and to inform the doctor if you feel a lump. Also, tell the doctor if a relative has or ever had breast cancer.

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult with the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link 'Report Side Effects of Drug Treatment' found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: <https://sideeffects.health.gov.il>

5) HOW SHOULD THE MEDICINE BE STORED?

- Prevent poisoning! This medicine, and any other medicine, must be kept in a safe place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) which appears on the package. The expiry date refers to the last day of that month.
- Store below 30°C.

6) FURTHER INFORMATION

- In addition to the active ingredient, the preparation also contains:
Polydimethylsiloxane elastomer, polydimethylsiloxane tubing, polyethylene containing 20-24% of barium sulphate, polyethylene pigmented with ≤ 1% of iron oxides and hydroxides (E172).
- What does the preparation look like and what are the contents of the package?
Mirena is designed in the shape of the letter *T*, so that the hormone is stored in a structure made from polydimethylsiloxane. The Mirena frame is white, made from polyethylene and also contains barium sulphate, and can therefore be seen in x-rays. Two brown, fine threads, made from iron oxide and polyethylene, attached to the bottom of the *T* shape, allow easier removal of the system and enable you and the doctor to ensure that the system is in the right place.
Each package contains one Mirena system packed in a sterile manner. Do not open before use.

Registration holder and address: Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 4527702.

Manufacturer and address: Bayer OY, Turku, Finland.

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