PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986
The medicine is dispensed with a doctor's prescription only

SAYANA®

Suspension for injection

Medroxyprogesterone acetate 104 mg/0.65 mL
Inactive ingredients and allergens: see section 2 "Important information regarding some of the ingredients of the medicine", 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 your treatment. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

1. WHAT IS THE MEDICINE INTENDED FOR?

- Sayana® is a long-acting contraceptive agent for women.
- In adolescent girls (12-18 years) Sayana® may be used only in circumstances where other contraceptive methods are unsuitable or unacceptable.
- Sayana® is given as a subcutaneous injection **once every three (3) months.**

Therapeutic group: Progesterone derivative
A progestogen derivative, which is chemically similar to the natural hormone progesterone (which is a natural female sex hormone). Progesterone is produced by the ovaries during the second half of the menstrual cycle. Sayana® prevents follicular maturation in the ovaries, as a result of which passage of an egg from the ovary to the uterus is prevented, and thus, fertilization is not possible and pregnancy is prevented.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- x You are sensitive (allergic) to the active ingredient or to any of the other ingredients contained in the medicine (see section 6).
- x You are pregnant or suspect you are pregnant.
- x You are suffering from unexplained vaginal bleeding.
- x You are suffering from a liver disease.
- x You have had, or there is a suspicion of, cancer of the breast or genital organs.
- x You are suffering, or have suffered in the past, from a disease affecting blood vessels of the brain.
- x You have a blood clot in a vein in your leg (deep vein thrombosis) or a blood clot that has travelled toward your lungs or another part of your body (an embolus).
- x You have problems with your circulation (e.g., pains in your legs or chest when you walk), or your blood clots too easily (thrombosis or embolism).
- x You suffer from thinning, softening or weakening of the bones.

Do not use the medicine without consulting a doctor before beginning treatment:
- If you are breastfeeding or are planning on breastfeeding.
- If you suffer, or have suffered in the past, from:
  - Migraines. If you start suffering from migraines after first use of the preparation, consult with the doctor before receiving further injections.
  - Diabetes or there is a family history of diabetes.
  - History of heart diseases or cholesterol problems, including a family history.
  - If you have recently had a "hydatidiform mole", a type of abnormal pregnancy.
  - History of depression.
  - Irregular, light or heavy menstrual bleeding.
  - An unusual breast x-ray, fibrocystic breast disease, lumps in the breast, bleeding from the nipples.
  - Stroke.
  - Family history of breast cancer.
  - Kidney disease.
  - Hypertension.
  - Asthma.
  - Epilepsy.
- If you are under the age of 18 (see under this section, below).

Sayana® may not be suitable for you if you suffer from any of these conditions.

Special warnings regarding use of the medicine:
Psychiatric disorders
Some women using hormonal contraceptives including Sayana® 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.

The effect of Sayana® on menstruation
Most users will experience a change in the nature of bleeding. It is likely that fewer women will experience irregular bleeding, and after 12 months of use, 60% will experience little or no bleeding at all.

Effect of Sayana® on bone mineral density
Sayana® acts by reducing the levels of estrogen and other hormones. However, low estrogen levels may lead to a reduction in bone mineral density. Women taking this preparation tend to have lower bone mineral density than women of the same age who have not used this preparation. This effect is at its peak in the first two-three years of using Sayana®. Afterwards, the level of bone mineral density stabilizes and it appears that there is a certain increase in bone mineral density upon discontinuing use of the medicine. It is still not known whether the use of Sayana® increases the risk of osteoporosis (weak bones) and fractures later in life (after the menopause).
The following are risk factors for developing osteoporosis later in life. Consult the doctor before starting the treatment; you may have to consider use of another contraceptive method if one of the following factors applies to you:
- chronic use of alcohol or tobacco
- chronic use of medicines that reduce bone mineral density such as treatment for epilepsy or steroids
- low body mass index (BMI) or eating disorders (anorexia or bulimia)
- a prior fracture not caused by falling
- a family tendency for osteoporosis

Adolescent girls (up to age 18): The bones of adolescent girls grow rapidly and become stronger. The stronger the state of the bones upon reaching puberty, the greater the protection against osteoporosis in the later stages of life. Use of Sayana® may lead to a reduction in bone mineral density during this important period. Bone strength increases again when treatment with Sayana® is discontinued, but it is not known if the same levels of bone mineral density as would have been reached had Sayana® not been used at all, are eventually reached.

Before using Sayana®, adolescent girls should discuss with the doctor whether another contraceptive measure would be more suitable for them.

During the course of treatment, it is recommended to regularly perform weight-bearing physical activity and to maintain a healthy diet that includes an adequate intake of calcium (e.g., dairy products) and vitamin D (e.g., fish).

Sayana® and possible risk of cancer
Studies in women who have used a range of medicine-based contraception showed that women who used injectable progesterone-based contraception, like Sayana®, had no increased risk of developing cancer of the ovary, womb, cervix, or liver.
Breast cancer is rare in women under the age of 40, but the risk of getting breast cancer increases with age.
There seems to be a slightly increased risk of breast cancer in women who use injectable contraceptives compared to women of the same age who do not use hormonal contraceptives.
This small extra risk of developing breast cancer has to be weighed against the known benefits of medicines like Sayana®. It is not certain whether the injection increases the risk of getting breast cancer. It may be that women receiving the injection are examined more often, and the disease is therefore detected earlier. Breast cancer seems less likely to spread in women taking preparations like Sayana® than in women who do not take these preparations.
The risk of finding breast cancer is not affected by duration of treatment with the preparation, but by the age at which use of the preparation is discontinued, since the risk of breast cancer increases with age. The risk of finding breast cancer is identical among women who stopped using hormonal contraceptives approximately 10 years ago and women who never took hormonal contraceptives.
In 10,000 women who used injections like Sayana® for up to 5 years, and stopped using the preparation before the age of 20, it is estimated that less than one additional case of breast cancer would occur up to 10 years after discontinuing use of the medicine, compared to 10,000 women who have never used the preparation.
In 10,000 women who used injections like Sayana® for 5 years and who stopped using the preparation before the age of 30, 2-3 extra cases of breast cancer will occur up to 10 years after discontinuing use of the medicine (in addition to the 44 cases in 10,000 women who have never used the preparation).
In 10,000 women who used injections like Sayana® for 5 years and stopped using the preparation before the age of 40, about 10 extra cases of breast cancer will occur up to 10 years after discontinuing use of the medicine (in addition to 160 cases in 10,000 women of this age who have never used the preparation).
Sayana® does not protect against HIV infection, e.g., AIDS, and other sexually transmitted infections. Safer sex practices, including correct and consistent use of condoms, reduce the transmission of sexually transmitted infections through sexual contact, including HIV (AIDS).
You should seek advice from your healthcare professional on how to decrease your risk of catching sexually transmitted infections including HIV (AIDS).

Sayana® and liver problems
If you develop jaundice (yellowing of the skin or eyes) while using Sayana®, consult the doctor before receiving further injections.

Effect of Sayana® on blood clotting
A blood clot can occur in the leg veins (deep vein thrombosis or DVT). Signs of a blood clot include redness, pain or swelling of the legs. If the clot moves toward the lungs (pulmonary embolism), the symptoms are chest pain, breathlessness, fainting and death. Symptoms of a blood clot in the eye may include sudden change in eyesight (sudden loss of vision or blurred vision). A blood clot can also form in the blood vessels of the brain, causing a stroke. Symptoms of a stroke include sudden and severe headache, slurred speech, weakness or numbness in the limbs, especially on one side. If you experience any of these symptoms, refer to the doctor immediately and refrain from continuing treatment with the medicine.

Tests and follow-up
Before starting to use Sayana® injections, you must undergo a thorough gynecological examination (including the breasts) and make sure you are not pregnant. The gynecological examination must be repeated every year.

Drug interactions
If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.
Especially, inform the doctor or pharmacist if you are taking:
- Anticoagulants.

If you are receiving treatment from any other doctor, make sure he/she is aware that you are using Sayana® as a contraceptive.

Pregnancy and breastfeeding
Do not use the medicine if you are pregnant. If you think you may have become pregnant during the course of treatment with this medicine, tell the doctor immediately.
Before taking the medicine, consult the doctor if you are breastfeeding or planning on breastfeeding.
If you are breastfeeding, the injection should be given no sooner than 6 weeks after giving birth, when the baby is more developed. The medicine can pass into breast milk, however no harmful effect on babies has been found.

Driving and use of machinery
No effects on the ability to drive or operate machines have been observed with use of this medicine.

Important information regarding some of the ingredients of the medicine
- Sayana® contains a negligible amount of sodium and is, therefore, considered sodium-free.
- Sayana® contains the substances methyl parahydroxybenzoate and propyl parahydroxybenzoate. These substances may cause allergic reactions (sometimes delayed reactions).

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor's instructions.
The dosage and treatment regimen will be determined by the doctor only. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.
Sayana® is given as a single subcutaneous 104 mg injection to the lower abdomen or the upper front part of the thigh every 3 months (12 to 13 weeks). Be sure to return to your doctor for the next injection.

First injection: To ensure that you are not pregnant at the time of the first injection, it is essential that your first injection be given **ONLY** during the first 5 days of your normal menstrual cycle. After giving birth: If you use Sayana® after giving birth and you are not breastfeeding, have the first injection administered within 5 days of delivery, or in the sixth week after giving birth, if you are breastfeeding.
There is evidence that women who use Sayana® immediately after giving birth or termination of a pregnancy can experience prolonged and heavy bleeding. Because of this, Sayana® should be used with caution at this stage.

Further injections: The subsequent doses of Sayana® will be given every 3 months (12 to 13 weeks), but no more than 14 weeks from the previous injection and regardless of the time and heaviness of the menstrual cycle. **It is important to receive your subsequent doses at the right time.**

If you have forgotten to receive Sayana® on time, or if more than 14 weeks have passed since the previous injection, there is a greater risk of you becoming pregnant. Consult the doctor regarding the appropriate time for receiving Sayana® and about the use of another contraceptive measure until the time of the injection.

Switching from another contraceptive method to Sayana®: When you switch from another contraceptive method, your doctor will make sure that you are not pregnant by administering the first injection of Sayana® at the appropriate time. If you have previously used oral contraceptives (pills), you should receive the first Sayana® injection within 7 days of taking the last active pill.

How can you help achieve optimal contraceptive efficacy while using Sayana®?
The efficacy of the Sayana® preparation for contraception is conditional upon your adherence to receiving an injection of the preparation at the appropriate time.
If more than 3 months have elapsed between injections, or more than 6 weeks after giving birth, you should be checked by your doctor before resuming use of Sayana® injections.

What should you do if you want to become pregnant while you are still under the long-term effect of the preparation?
Your usual level of fertility will return when the effect of the last injection has worn off. The time this takes varies in different women, and does not depend on how long you have been using Sayana®.
In most women, the effect of Sayana® will wear off within 5 to 6 months after the last injection. Over 80% of women will get pregnant within a year of stopping Sayana® use. You may also already get pregnant in the first month after missing an injection.

Do not exceed the recommended dose!

If you took an overdose, or if a child has accidentally swallowed the medicine, proceed immediately to a hospital emergency room, and bring the package of the medicine with you.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take the medicine. Wear glasses if you need them.
If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of the medicine may 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.

Contact the doctor immediately if you experience any of the following serious side effects:
- A serious allergic reaction (unknown frequency). The symptoms include sudden wheezing, breathing difficulties or dizziness, swelling of the eyelids, lips, throat or face, hives (urticaria), skin rash. An allergic reaction may happen soon after the injection or can develop after a certain period of time.
- A blood clot in the lungs (unknown frequency). The symptoms are:
  - a sudden and unusual cough (may bring up blood)
  - severe pain in the chest which may increase with deep breathing
  - sudden unexplained breathlessness or rapid breathing
  - severe light headedness or dizziness
  - rapid or irregular heartbeat
  - severe abdominal pain.
- A blood clot in the leg (unknown frequency). The symptoms include: severe pain or swelling in one of the legs or feet that may be accompanied by tenderness, warmth or discolored skin.
- A blood clot in the eye (unknown frequency). The symptoms include: loss of vision, pain and swelling of the eye, especially if sudden.
- A stroke (unknown frequency). The symptoms include:
  - weakness or numbness of the face, arm or leg, especially on one side of the body
  - sudden confusion, trouble speaking or understanding
  - sudden trouble seeing in one or both eyes
  - sudden trouble walking, dizziness, loss of balance or coordination
  - sudden, severe or prolonged headache with no known cause
  - loss of consciousness or fainting, with or without seizures.

<u>Additional side effects</u>:

Additional common side effects (frequency of up to 1 in 10 patients):
Weight gain, abdominal pain (cramps), nausea, acne, amenorrhea (absence of menstrual bleeding or light bleeding), heavy bleeding, frequent and/or unexpected bleeding, irregular bleeding, menstrual pains, depression, tiredness, breast pain or tenderness, headache, decreased libido, mood changes, irritability/restlessness, difficulty sleeping, anxiety, vaginal itching or irritation, injection site reaction (including pain, tenderness, swelling, persistent skin indentation/dimpling), dizziness, back pain, limb pain, abnormal cervical smear.

Additional uncommon side effects (frequency of up to 1 in 100 patients):
Drug sensitivity, hirsutism (abnormal hairiness), feeling bloated, fluid retention, vaginal discharge, vaginal dryness, pain during sexual intercourse, ovarian cyst, hypertension, pelvic pain, premenstrual syndrome, change in breast size, milky discharge from breasts (when you are not breastfeeding), change in appetite, muscle cramps, joint pain, sleepiness, migraine, vertigo, hot flushes, fever, rapid heart rate, varicose veins, lesions/bruises, facial skin discoloration, rash, itching, hair loss, skin irritation, hives, inflammation of the veins (felt as tenderness or redness in the area), nervousness, reduced bone mineral density (there is a test used to diagnose osteoporosis or weak bones), decreased glucose tolerance (increase in sugar level in the blood), emotional disturbance, inability to achieve a sexual climax, abnormal liver function blood test results.

Rare side effects (frequency of up to 1 in 1,000 patients):
Breast cancer, weakness, weight loss, deformation of skin at the injection site.

Side effects of unknown frequency:
Osteoporosis (bone thinning) including fractures, seizures, skin stretch marks, abnormal liver function (such as yellowing of the skin or eyes, jaundice).

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the 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?

Store below 25°C.
Do not store in the refrigerator or freeze.
After opening, use immediately.
Discard the remnants of the preparation after use, in accordance with the required guidelines.
Do not reuse the needle and syringe.
Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Macrogol 3350, sodium chloride, povidone, polysorbate 80, methyl parahydroxybenzoate, propyl parahydroxybenzoate, methionine, monobasic sodium phosphate, disodium phosphate dodecahydrate, hydrochloric acid and/or sodium hydroxide for pH adjustment, water for injection.

What the medicine looks like and the contents of the package:
Sayana®: a white to off-white suspension for injection in a pre-filled syringe.

Manufacturer: Pfizer NV/SA, Puurs, Belgium.

License Holder: Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Sayana®: 143-81-32952
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