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

The medicine is dispensed with a doctor's prescription only

Depo-Provera® 150 mg/ml

Suspension for injection

Medroxyprogesterone acetate 150 mg/ml

Inactive and allergenic ingredients: see section 2 under "Important information about some of the ingredients of the medicine" and section 6 "Further information".

Read the 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 to treat you. 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.

The effectiveness of Depo-Provera® in the prevention of pregnancy depends on your adherence to receiving an injection of the preparation once every 12 weeks.

1. WHAT IS THE MEDICINE INTENDED FOR?

- Depo-Provera® is a contraceptive agent, when there is a medical indication for this and oral contraceptives (taken by mouth) cannot be used.

Therapeutic group:
Progestogens

A progesterone derivative – Depo-Provera® contains the active ingredient medroxyprogesterone acetate, which is chemically similar to the natural hormone progesterone. Progesterone is produced by the ovaries during the second half of the menstrual cycle. Depo-Provera® prevents the eggs in the ovaries from maturing, thereby preventing their passage from the ovaries into the womb, and therefore, fertilization is not possible and pregnancy is prevented. Depo-Provera® also acts by changing the lining of the womb, which makes it less likely for pregnancy to occur, and by thickening the mucosa at the entrance of the womb, making it more difficult for sperm to enter.

Depo-Provera® is given as an intramuscular injection **once every 12 weeks**.

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 additional ingredients contained in the medicine (see section 6). There is a small risk of a severe allergic reaction to Depo-Provera®, which would require emergency medical treatment.
- x You are pregnant or there is a possibility that you are pregnant.
- x You have had or think you may have hormone-dependent cancer of the breast or reproductive organs.
- x You suffer from unexplained bleeding from the womb.
- x You suffer from liver disease.
- x You have not yet had your first period.

Special warnings regarding use of the medicine

Before treatment with Depo-Provera®, tell the doctor if you suffer or have suffered in the past from:

- Migraines – if you develop migraine, you should consult your doctor before receiving further injections of Depo-Provera®
- Diabetes or a family history of diabetes
- Severe pain or swelling in the calf (indicating a possible blood clot in the leg, which may be called phlebitis)
- Blood clotting disorders such as deep vein thrombosis (blood clot in the leg), pulmonary embolism (blood clot in the lung) or a stroke; it is recommended that you do not receive further injections of Depo-Provera®
- Visual disturbances while using Depo-Provera®, such as a sudden partial or complete loss of vision or double vision
- Depression or a history of depression
- Liver problems or liver disease
- Kidney problems or kidney disease
- A history of heart disease or cholesterol disturbances, including a family history
- You have recently had a 'hydatidiform mole', which is a type of abnormal pregnancy
- Asthma
- Epilepsy
- You are using certain medicines such as high-dose glucocorticoids (steroids), anti-epileptics, and thyroid hormones, your doctor may recommend a more suitable type of contraception for you.

Psychiatric illnesses

Some women using hormonal contraceptives, including Depo-Provera®, 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.

Possible effect on your periods

Depo-Provera® will usually affect the pattern of a woman's period. After the first injection it is most likely that you will have irregular, possibly lengthy bleeding or spotting. This will continue in some women, and is considered to be normal and nothing to worry about.

One third of women will not have any bleeding at all after the first injection. After 4 injections, most women find that their periods have stopped completely. Not having periods is nothing to worry about.

If you experience very heavy or prolonged bleeding, you should consult with your doctor. This happens rarely but can be treated.

After you stop taking Depo-Provera®, your periods will return to normal within a few months.

Possible effect on bone density

Depo-Provera® works by lowering levels of estrogen and other hormones. However, lower estrogen levels can cause bones to become thinner (by reducing bone density). Women who use Depo-Provera® tend to have lower bone density than women of the same age who have never used it. The effect of Depo-Provera® peaks in the first 2-3 years of use. Following this, the bone density level stabilizes and there appears to be some increase in bone density when use of the medicine is stopped. It is still not known whether Depo-Provera® increases the risk for osteoporosis (weak bones) and fractures in later life (after menopause).

The following are risk factors for the development of osteoporosis in later life. You should consult with your doctor before starting treatment, as the use of a different contraceptive may be need to be considered if any of the following factors are relevant to you: chronic alcohol or tobacco use, chronic use of medicines that reduce bone density such as medicines to treat epilepsy or steroids, low body mass index (BMI) or eating disorder (anorexia or bulimia), previous trauma fracture that was not caused by a fall, strong familial tendency to osteoporosis.

Teenagers (up to 18 years of age)

Usually, the bones of teenagers grow rapidly and increase in strength. The stronger the bones are when adulthood is reached, the greater the protection against osteoporosis in later stages of life. The use of Depo-Provera® may cause decreased bone density during this important period in which the bones should be growing, so the effect of this medicine is particularly important in this age group. Bone strength increases again when treatment with Depo-Provera® is stopped, but it is not known whether the levels of bone density ultimately reached are the same as would have been achieved if Depo-Provera® were never used. **Before using Depo-Provera®, teenagers should discuss with the doctor the question of whether another form of contraception is more suitable.**

During treatment with Depo-Provera®, it is recommended to carry out regular weight-bearing exercise and to maintain a healthy diet, including an adequate amount of calcium (e.g., dairy products) and vitamin D (e.g., from fish oil).

Possible risk of cancer

Studies of women who have used different forms of contraception showed that in women who used Depo-Provera®, no increase was observed in the overall risk of developing cancer of the ovary, womb, cervix or liver.

Possible risk of breast cancer

Breast cancer is rare among women under 40 years of age, whether or not they use hormonal contraceptives. Depo-Provera® increases the risk of breast cancer slightly compared with women who have never used it. However, any increased risk is small in relation to the overall risk of breast cancer, particularly in young women.

In older women, the risk of breast cancer is higher, and therefore the increase in the number of cases due to Depo-Provera® is larger in older women than in young women.

For example:

A 15-year-old girl who uses Depo-Provera® for 5 years, the increase in the chance of developing breast cancer by the age of 30 is negligible.

A 25-year-old woman who uses Depo-Provera® for 5 years increases her chance of developing breast cancer by the age of 40 from 44 cases per 10,000 women (who did not use Depo-Provera®) to 47 cases per 10,000 women, i.e., an increase of 3 cases per 10,000 women.

A 35-year-old woman who uses Depo-Provera® for 5 years increases her chance of developing breast cancer by the age of 50 from 160 cases per 10,000 women (who did not use Depo-Provera®) to 170 cases per 10,000 women, i.e., an increase of 10 cases per 10,000 women.

Possible risk of forming an abscess (puss) at the injection site

As with any intramuscular injection, there is a risk of an abscess forming at the site of injection. This may require medical or surgical attention.

Possible risk of weight gain

Some women gained weight while using Depo-Provera®. Studies have found that over the first two years of use of Depo-Provera®, there was a weight gain of 2.3-3.6 kg. Women who completed 4-6 years of treatment gained an average of 6.4-7.5 kg.

Cervical smear testing

The results of a cervical smear and some additional laboratory tests could be affected during treatment with Depo-Provera®, so it is important to inform your doctor that you are using the medicine.

Protection against sexually transmitted infections

Depo-Provera® does not protect against catching HIV infection (AIDS) or against other sexually transmitted infections.

Safe sex practices, including the correct and consistent use of condoms, reduce the transmission of sexually transmitted infections through sexual contact, including HIV (AIDS).

Consult with the doctor, nurse or pharmacist on how to decrease your risk of catching sexually transmitted infections, including HIV.

Tests and follow-up

Your doctor may ask you about your and your family's medical conditions, check your blood pressure and rule out the possibility that you are pregnant. Additional examination, such as breast examinations, may be needed, only if these examinations are needed for you or if you are unusually concerned.

Drug interactions

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

Aminoglutethiamide or other medicines that thin your blood (anticoagulants) as these may affect the way Depo-Provera® works.

Pregnancy, breast-feeding and fertility

Pregnancy:

Do not use Depo-Provera® if you are pregnant, as medicine containing hormones can affect the developing baby.

If you think you have become pregnant while using Depo-Provera®, tell the doctor immediately. Before giving you the first injection and if any additional injection is delayed beyond 89 days (12 weeks and 5 days), the doctor will check that you are not pregnant.

Fertility:

- Your usual level of fertility should return when the effect of the injection has worn off. This takes different amounts of time in different women, and does not depend on how long you have been using Depo-Provera®.
- In studies, it was found that over 80% of women trying to get pregnant conceived within 15 months of the last injection; however, this varied from 4 months after the last injection to more than two years.
- Some women got pregnant as early as 14 weeks after their last injection.

Breast-feeding:

Depo-Provera® does not prevent the breast from producing milk, so nursing mothers can use it. However, it is better that in the first few weeks after birth, breast milk should not contain any medicines, including Depo-Provera®.

If you are breast-feeding, your doctor may advise to wait at least 6 weeks after childbirth before you start using Depo-Provera® for contraception.

No harmful effects have been observed in infants and children who have been exposed to Depo-Provera® in breast milk.

Driving and operating machinery

Depo-Provera® may cause headaches and dizziness. Therefore, be careful until you know whether this medicine affects your ability to drive or operate machinery. If you are unsure, consult a doctor.

Important information about some of the ingredients of the medicine

Depo-Provera® contains methylparaben, propylparaben and sodium

Methylparaben and propylparaben may cause allergic reactions (possibly delayed) and, exceptionally, bronchospasm.

The medicine contains less than 1 mmol sodium (23 mg) per 150 mg/ml; it is essentially "sodium free".

3. HOW SHOULD YOU USE THE MEDICINE?

Always use according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the medicine.

The dosage and treatment regimen will be determined by the doctor only.

Depo-Provera® is given as a single intramuscular injection of 1 ml (150 mg medroxyprogesterone acetate) into the muscle of the upper arm or the buttock every 12 weeks.

Women commencing the use of Depo-Provera® for the first time should have the preparation injected within the first 5 days of their menstrual period or within 5 days after childbirth if they are **not** breast-feeding.

Provided that the medicine is given in accordance with the instructions, you are protected from pregnancy straight away and there is no need to use an additional contraceptive.

Depo-Provera® works as a contraceptive for 12 weeks in your body. Once the injection has been given, its effect cannot be reversed.

For effective contraceptive cover, Depo-Provera® must be given every 12 weeks. Be sure to make an appointment with the doctor every 12 weeks.

The risk of heavy or prolonged vaginal bleeding may be increased if Depo-Provera® is used immediately following childbirth or termination of pregnancy.

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.

If you forget to take the medicine

If you forgot to receive your injection or more than 12 weeks have passed since your previous injection, there is a greater chance that you could become pregnant. Consult the doctor regarding when you can get the next Depo-Provera® injection and regarding other contraceptive to use until the next injection.

Switching from another method of contraception

When you switch from another contraceptive method, your doctor will give you the first injection at the appropriate time to ensure that you are not at risk of becoming pregnant. If you are switching from using pills, you should have your first injection of Depo-Provera® within 7 days after taking your last pill.

Adhere to the treatment regimen as recommended by the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take 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 notice any of the following side effects:

- Hypersensitivity (allergic) reaction (it is not known how frequently this occurs). Symptoms include: sudden skin rash, swelling of the face, lips, tongue or throat, wheezing or difficulty in breathing
- Blood clot in the lungs (occurs **rarely** – appears in up to 1 in 1,000 users). Symptoms include:
  - Shortness of breath
  - Breath-related chest pains
  - Coughing up blood
- Blood clot in the leg (occurs **rarely** – appears in up to 1 in 1,000 users)
- Deep vein thrombosis (DVT) is a condition in which a blood clot forms in one of the deep veins, usually in the leg. Symptoms of **deep vein thrombosis** include:
  - Pain, tenderness or swelling in the calf, ankle or foot
  - Painful or tender veins in the leg
  - Difficulty putting your full body weight on the affected leg
  - Purple discoloration of the leg, or the skin becomes red and warm to touch
- Jaundice (yellowing of the skin or whites of the eyes)

Women who use Depo-Provera® tend to have lower bone density than women of the same age who have never used it. The effects of the medicine are greater in the first 2-3 years of use. Following this, bone density stabilizes and there appears to be some recovery after the use of the medicine is stopped. It is not yet possible to determine whether Depo-Provera® increases the risk of osteoporosis (weak bones) and fractures at older ages.

Additional side effects:

Very common side effects: occur in more than 1 user in 10

Irritability, headache, abdominal pain or discomfort, changes in body weight.

Common side effects: occur in up to 1 user in 10

Depression, reduced libido (decreased sex drive), dizziness, nausea, feeling bloated, hair loss, acne, back pain, vaginal discharge, breast tenderness, painful or difficult menstrual period, urinary tract infection, edema/fluid retention, weakness, painful limbs.

Uncommon side effects: occur in up to 1 user in 100

Increased or decreased appetite, difficulty sleeping, convulsions (fits), drowsiness, tingling, hot flushes, liver disorder, growth of facial hair, nettle rash or hives, itchy skin, temporary brown patches, unexpected or unusual vaginal bleeding or spotting, secretion of milk from the breasts when not pregnant or breast-feeding, pelvic pain, painful intercourse, cessation of secretion of milk in breast-feeding women.

Rare side effects: occur in up to 1 user in 1,000

Breast cancer, reduction in red blood cells, blood disorders, difficulty reaching orgasm, behavioral change, mood change, irritability, anxiety, migraine, paralysis, fainting, feeling of dizziness or spinning, rapid pulse, hypertension, varicose veins (prominent veins), anal bleeding, indigestion, liver enzyme disorder, accumulation of fat (at the injection site), inflammation of the skin, formation of scar tissue, stretch marks, joint pain, muscle cramps, reduced bone density (osteoporosis), vaginal pain or inflammation, stopping or extended break in menstrual periods, chest pain, bleeding or increased bleeding from the womb, menstrual period with heavier or more prolonged bleeding than usual, vaginal dryness, change in breast size, ovarian or vaginal cysts, premenstrual syndrome, increased thickness of the lining of the womb, breast lumps, bleeding from the nipple, delayed ovulation and long menstrual period, feeling pregnant, fever, tiredness, pain or tenderness at the injection site, lump or dimple at the injection site, feeling thirsty, hoarseness, facial nerve paralysis, decreased sugar tolerance, abnormal cervical smear, skin color changes, enlarged lymph nodes.

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 may be reported to the Ministry of Health by clicking 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.

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.

Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:

Polyethylene glycol 3350, Sodium chloride, Polysorbate 80, Methyl paraben, Propyl paraben, Sodium hydroxide, Hydrochloric acid, Water for injection.

What the medicine looks like and the contents of the package:

Depo-Provera® 150 mg/ml: A pre-filled syringe with 1 ml of white sterile suspension.

License Holder and Address: Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzeliya Pituach 46725.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:

Depo-Provera® 150 mg/ml: 069.69.24309

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