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

The medicine is dispensed with a doctor's prescription only

Progynova 2 mg
Coated Tablets

Active ingredient and its concentration in each tablet:
Each tablet contains:
Estradiol Valerate 2 mg.
Inactive ingredients and allergens: 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 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.

ESSENTIAL INFORMATION ABOUT PROGYNOVA
- Progynova is not a contraceptive pill.
- Progynova is an estrogen-only hormone replacement therapy (HRT), intended for postmenopausal women.
- In section 2, subsection "Medical conditions which require close medical surveillance during HRT" medical conditions are detailed, which, if they apply to you, you must make sure to be under frequent medical surveillance. It is important that you read this information carefully.
- In section 3 "How should you use the medicine?", there are details of when treatment with Progynova should be initiated and if it is advisable to receive a progesterone supplement.

1) WHAT IS THE MEDICINE INTENDED FOR?
The medicine contains estrogen, one of the female sex hormones, and is intended to treat women who suffer from deficiency of this hormone, as a result of menopause or for any other reason.
Therapeutic group: Estrogens.

2) BEFORE USING THE MEDICINE:
Do not use the preparation if:
- you have ever had, have or suspect that you have breast cancer
- you are currently suffering from, or you may possibly have estrogen-sensitive cancer, such as cancer of the womb lining
- you have unexplained vaginal bleeding
- you have excessive thickening of the womb lining, that is not being treated
- you have or have ever had formations of blood clots in the veins (thrombosis), such as in the veins of the lungs or legs
- you have a blood clotting disorder (such as protein C, protein S or antithrombin deficiency)
- you have or have recently had a disease caused by blood clots in the arteries, such as: a heart attack, stroke or angina pectoris
- you have or have ever had, a liver disease and your liver functions are abnormal
- you have a rare hereditary blood disease, porphyria
- you are sensitive (allergic) to the active ingredient or to any of the other ingredients contained in the medicine, see section 6 for inactive ingredients in the medicine
- you are pregnant, think you are pregnant or are breastfeeding, see subsection "Pregnancy and breastfeeding"
- you have been told to refrain from lactose, if you have an hereditary condition called lactose intolerance or glucose-galactose malabsorption

If any of the above conditions appears for the first time after you start taking the medicine, stop taking it and consult your doctor immediately.

This medicine does not prevent pregnancy. If 12 months have not elapsed from your last menstruation or you are less than 50 years old, you may need to use an additional contraceptive in order to prevent pregnancy. Consult with the doctor.

Before treatment with Progynova, tell the doctor if:

Medical conditions which require close medical surveillance during HRT
Before starting treatment, tell your doctor if you have had any of the problems detailed below, as these may recur or worsen during the course of treatment with Progynova. In such a case, you will have to come for medical monitoring frequently.
Fibroids (myomas) inside the womb, growth of the womb lining outside the womb (endometriosis) or if you have a history of excessive thickening of the womb lining (endometrial hyperplasia), increased risk of developing blood clots (see in "Blood clots in the veins (thrombosis)" section), increased risk of developing an estrogen-sensitive cancer (such as a mother, grandmother or sister who has had breast cancer), high blood pressure, liver function disorders, such as benign liver tumors, diabetes, gallstones, migraine or severe headache, lupus, epilepsy, asthma, a disease affecting the eardrum and hearing (otosclerosis), very high levels of fat in the blood (triglycerides), fluid retention due to cardiac or kidney problems.

HRT and cancer

- **Excessive thickening of the lining of the womb (endometrial hyperplasia) or endometrial cancer**

Taking estrogen-only hormone replacement increases the risk of endometrial hyperplasia and of endometrial cancer. A progesterone supplement, for at least 12 days of each 28-day cycle, will protect you from this extra risk. If you still have your womb, your doctor will prescribe progesterone separately. If your womb has been removed, consult with your doctor as to whether you can take this medicine without progesterone. If your womb has been removed because of endometriosis, you may still be at risk and therefore, your doctor may add progesterone to the estrogen.

- **Breast cancer**

Evidence suggests that treatment with combined estrogen-progesterone, and possibly also estrogen-only, increases the risk of breast cancer. The increased risk depends on how long you use HRT. The increased risk becomes evident within a few years. However, after discontinuation of treatment, seemingly after five years at most, the risk is equal to that of the general population. For women who have had their womb removed and who are treated with estrogen-only hormone replacement, an increased risk of breast cancer was practically not observed.
The risk of developing breast cancer also increases if you have a close relative (mother, sister or grandmother) who has had breast cancer or if you are seriously overweight.

Be sure to regularly check your breasts. Refer to the doctor if you notice any of the following signs: Changes in the shape of the breast, dimpling in or bumps on the skin, changes in the nipple or if you feel or see lumps.
In addition, you are advised to undertake mammography screening. Before the examination, it is important that you inform the nurse or healthcare professional who is performing the test that you are taking medicines for HRT, as this medicine may increase the density of your breasts which could affect the outcome of the examination. When the density of the breast is increased, mammography screening may not detect all lumps.

- **Ovarian cancer**

Ovarian cancer is rare, much more rare than breast cancer. It is difficult to diagnose because there are often no obvious signs of the disease. The use of estrogen alone, or combined estrogen-progesterone HRT slightly increases the risk of ovarian cancer.

Effects of HRT on the heart or circulation

- **Blood clots in the veins (thrombosis)**

The risk of blood clots in the veins (DVT) is 1.3 to about 3–times higher in women who take HRT, in comparison to women who do not take HRT, especially during the first year of treatment. Blood clots can be serious if they reach the lungs, and can cause chest pains, breathlessness, fainting and even death. This condition is called pulmonary embolism. DVT and pulmonary embolism are examples of venous thromboembolism (VTE).
The risk of blood clots rises with age or if you have one of the risk factors described here. Tell the doctor if any of these situations apply to you: you are unable to walk because of major surgery you underwent (see information relating to "If you are due to undergo surgery" in section 3), injury or illness; you are seriously overweight (BMI >30 kg/m^2); if you suffer from blood clots and you are under long-term treatment with a medicine used to prevent blood clots; any of your first-degree relatives (parents, siblings) has ever had a blood clot in the lung, legs or any other organ; you have had one or more spontaneous miscarriages; you have lupus or cancer.
The signs of a blood clot can be: painful swelling and redness of the legs, sudden chest pain, difficulty breathing.

- **Heart disease (heart attack)**

There is no evidence that HRT will prevent a heart attack. HRT is not recommended for women who have a heart disease or have recently had a heart disease. If you have ever had a heart disease, consult with your doctor whether HRT is suitable for you. Women over the age of 60, treated with combined estrogen-progesterone HRT are at slightly higher risk of developing heart disease than women that have not been treated with HRT. For women who have had their womb removed and who are taking estrogen-only hormone replacement, there is no increased risk of developing heart disease.

Pay attention if you get a pain in the chest that radiates to the arm or neck. This pain may be a sign of a heart attack. Refer to the doctor immediately and do not continue treatment until the doctor tells you that you can continue.

- **Stroke**

The risk of getting a stroke is 1.5–times higher in HRT users than in non–users. The risk of getting a stroke among HRT users increases with age. Additional risk factors for stroke are: hypertension, smoking, drinking too much alcohol, irregular heartbeats. If you have any of the detailed risk factors or if you have had a stroke in the past, consult with your doctor whether the treatment is suitable for you.

Additional warnings regarding the medicine
- HRT does not prevent memory loss. There is evidence that there is an increased risk of memory loss in women who started HRT after the age of 65. Consult with your doctor.
- If you have a tendency to develop brown patches on the skin of your face, avoid exposure to the sun or ultraviolet (UV) light while using Progynova.
- If you have elevated blood triglyceride levels, the doctor should monitor your triglyceride levels frequently during the course of HRT. Rare cases of sharp increases in triglyceride levels leading to pancreatitis, as a result of HRT, have been reported
- If you have a heart or kidney problem, your doctor should examine you thoroughly, in order to identify a possibility of fluid retention and swelling which may be caused by estrogen.
- Your doctor will have to monitor you frequently if you have terminal kidney insufficiency, as the blood levels of the active ingredient, estradiol, will probably increase.

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. It is especially important to inform the doctor or pharmacist if you are taking:
- medicines intended for treatment of epilepsy (such as: barbiturates, phenytoin, primidone, carbamazepine, oxcarbazepine, topiramate and felbamate)
- medicines for treatment of the AIDS virus (HIV) and hepatitis type C virus infections (called protease inhibitors and non-nucleoside analog reverse transcriptase inhibitors such as: nevirapine, efavirenz, ritonavir, nelfinavir)
- medicines for treatment of tuberculosis (such as: rifampicin and rifabutin)
- nutritional supplements or herbal remedies that contain St. John's wort (Hypericum).
- medicines for the treatment of fungal infections (such as: griseofulvin, fluconazole, itraconazole, voriconazole and ketoconazole)
- medicines for the treatment of bacterial infections (such as: clarithromycin and erythromycin)
- Medicines for treatment of certain heart diseases, high blood pressure (such as verapamil and diltiazem)
- Grapefruit juice

These medicines may interfere with the effect of Progynova and cause irregular bleeding.

Pregnancy and breastfeeding
The medicine is intended for post-menopausal women only. Please see subsection "Do not use the preparation if:" Do not take this medicine if you are pregnant or breastfeeding. If you became pregnant during the course of treatment, stop the treatment immediately and refer to the doctor.

Driving and use of machines
No effects of Progynova on driving and operating machinery have been observed.

Important information regarding some of the medicine's components
- Progynova contains lactose. Each tablet contains: 46 mg lactose monohydrate. If you have an intolerance to lactose, consult with the doctor before taking the medicine.
- Each Progynova tablet also contains: 33.5 mg sucrose (see section 6 "Further Information").

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.
The dosage and treatment regimen will be determined by the doctor only.
- The usual dosage is generally one pill per day, every day, at a set time, for 28 days.

Do not exceed the recommended dose.
- The days of the week are indicated on the inner Progynova package (blister). In order to make it easier for you to remember to take the medicine each day, take the first tablet from the section marked with the first day. For example, if you began taking Progynova on Tuesday, take out the tablet next to where "TUE" is marked.
- When you have completed the pack of 28 tablets, carry on to the next pack, without stopping.
- Swallow the medicine whole with a glass of water or milk. The medicine can be taken with or without food.
- The doctor may also prescribe progesterone, in addition to Progynova, for at least 12-14 days of each month, if: you still have a womb or if you have a history of endometriosis.
- The tablet must not be crushed/halved/chewed.

Progynova must not be used in children and adolescents and in premenopausal women.

When to start treatment
If you are taking another HRT carry on with the treatment until you have finished your current monthly pack. Take your first Progynova tablet the next day, without taking a break between the previous medicine and Progynova.

If this is your first HRT treatment and your periods have become very infrequent or have stopped completely, you can start taking Progynova tablets on any day you choose, as long as you are sure you are not pregnant.

Tests and follow up:
If you have to have laboratory tests performed during the course of treatment with Progynova, be sure to inform the medical staff that you are taking Progynova, as the medicine may affect the results of certain laboratory tests.

Medical history and regular check-ups
The use of HRT, of any kind, carries risks which need to be considered before deciding to start taking it, or whether to carry on taking it.
Experience in the treatment of women with premature menopause (as a result of ovarian failure or surgery) is limited.
If you have experienced a premature menopause, the risks associated with HRT may vary. Please consult with your doctor.
Before you start or resume HRT, your doctor will ask you about your and your family's medical history. In addition, the doctor may decide to perform a physical examination, which includes the breasts and/or an internal examination.
Once you have started treatment with Progynova, you should see your doctor for regular check-ups (at least once a year). At these periodic check-ups, it is recommended that you discuss with your doctor the benefits and risks of continued treatment with HRT.

Be sure to:
- go for periodic breast (mammography) and cervical screening tests, as recommended by your doctor.
- perform a self-examination of your breasts for any changes, such as changes in the shape of the breast or nipple.

If you took more Progynova than recommended, you may feel nauseous, vomit and may even have some menstruation-like bleeding. No specific treatment is necessary, but consult with your doctor or pharmacist if you are concerned.

If you forget to take Progynova and less than 12 hours have elapsed from the set time of the day, take it as soon as you remember. Take the next tablet at the usual time.
If more than 12 hours have elapsed, leave the forgotten tablet in the pack. Continue to take the rest of the tablets at the usual time. You may experience sudden bleeding.
Adhere to the treatment regimen recommended by the doctor.
If you stopped taking Progynova, you may once again experience signs of menopause, including, hot flashes, sleep disturbances, nervousness, dizziness or vaginal dryness. Consult with your doctor or pharmacist before you decide to stop treatment.

If you are due to undergo surgery, tell the surgeon that you are taking Progynova. You may need to stop taking Progynova 4 or 6 weeks before the operation, in order to reduce the risk of a blood clot (see section 2, subsection "Blood clots in the veins (thrombosis)"). Consult the attending doctor regarding continued treatment after the operation.
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 Progynova 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.

Discontinue use of the medicine and refer to the doctor immediately if:
- you experience one or more of the effects mentioned in section 2, subsection "Do not use the preparation if:"
- you notice yellowing of the skin or whites of the eyes (jaundice). These can be signs of a liver disease.
- you experience a sharp increase in blood pressure (can be manifested by headache, fatigue, dizziness).
- you experience migraine-like pains, that did not exist previously.
- you become pregnant.
- you notice signs that indicate a blood clot, such as: painful swelling and redness of the legs, sudden chest pain, breathing difficulties (further details in section 2).

The following diseases occur more often in women treated with HRT, when compared to women who are not treated with HRT:

Serious side effects
Breast cancer, abnormal thickening or cancer of the lining of the womb, ovarian cancer, blood clots in the veins of the legs or lungs, heart disease, stroke, memory loss if you started treatment after the age of 65.
For more information about these effects, see section 2.

Additional side effects that have been linked to the use of Progynova and other HRTs:
- During the first few months of treatment, you may experience some unexpected bleeding. This is expected to pass with continued treatment. If it does not, contact your doctor (see section 2, subsection "Excessive thickening of the lining of the womb (endometrial hyperplasia) or endometrial cancer").
- breast pain, tenderness or enlargement, breast discharge
- painful period, changes in vaginal discharge, premenstrual syndrome, development of fibroids (myomas) in the womb, thrush, changes to the neck of the womb
- indigestion, a feeling of being bloated, flatulence, nausea, abdominal pain, gallbladder diseases
- skin rash or discoloration, itching, eczema, acne, unusual hair loss or hair growth, increased skin pigmentation, particularly on the skin of the face (see section 2, subsection "Additional warnings regarding the medicine" for more information), rare skin diseases
- headaches, migraines, dizziness, anxiety or signs of depression, fatigue
- fast or irregular heartbeats (palpitations), high blood pressure, inflammation of veins, primarily in the legs
- fluid retention, manifested by edema and swelling of body parts
- changes in body weight and sex drive, increased appetite
- muscle cramps, leg pain
- nosebleed, visual disturbances (such as blurred vision), discomfort with contact lenses, allergic reactions, decrease of glucose tolerance, bladder inflammation, rare disorders (porphyria, chorea)

The following side effects have been reported with other HRTs: various skin disorders, such as: painful and reddish swelling, rash with a defined shape or sores.
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://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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.

5) HOW SHOULD THE MEDICINE BE STORED?
- Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach 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) that appears on the package. The expiry date refers to the last day of that month.
- Store at a temperature below 25°C.

6) FURTHER INFORMATION
- In addition to the active ingredient, the medicine also contains:
  The tablet:
  Lactose monohydrate, maize starch, polyvidone 25000, talc, magnesium stearate.
  The coating:
  Sucrose, polyvidone 700000, macrogol 6000, calcium carbonate, talc, glycerol 85%, titanium dioxide (E171), indigo carmine (E132), montanglycol wax.
- Each Progynova tablet contains: 33.5 mg sucrose and 46 mg lactose monohydrate.
- What does the medicine look like and what are the contents of the package: The tablets are blue, coated, round and biconvex.
  The package contains 28 tablets arranged in a blister.
- Registration Holder and address: Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240.
- Manufacturer and address: Bayer Weimar GmbH und Co. KG, Weimar, Germany.
- This leaflet was checked and approved by the Ministry of Health in 30.04.2017
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
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