Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Progyluton

Tablets

Active ingredients:

Each of the 10 light brown tablets contains:

estradiol valerate 2 mg

norgestrel 0.5 mg

Each of the 11 white tablets contains:

estradiol valerate 2 mg

Inactive ingredients and allergens: see section 6 "Additional information" and section 2 "Important information about some of this medicine's ingredients".

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your 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 to yours.

Attention:

Progyluton is not a contraceptive (see "Special warnings about using this medicine").

Hormone replacement therapy (HRT) may be associated with a higher risk of developing certain diseases such as breast cancer, cardiovascular diseases (heart attack, stroke, venous thrombosis and pulmonary embolisms - development of blood clots in blood vessels) (see "Special warnings about using this medicine"). Your doctor will weigh up the risks of hormone therapy compared with the expected benefits and will discuss them with you.

1) What is this medicine intended for?

A hormonal medicine in two phases to treat irregularities of the menstrual cycle and peri-menopausal disturbances.

Therapeutic group: Hormone Replacement Therapy (HRT) - estrogen and progestogen.

Each tablet contains a small amount of two female hormones: estrogen (estradiol valerate) and progestogen (norgestrel).

During menopause and in the period preceding it, estrogen production by the woman's body gradually decreases, which may cause menstrual cycle irregularities, hot flushes, night sweats, mood swings and dryness in the vagina. In the long term, thinning of the bones (osteoporosis) may also occur.

Progyluton serves as a substitute for estrogen during menopause and in the period preceding it, and thereby improves the symptoms which may appear. The additional hormone in Progyluton is progestogen, which contributes to regulation of the bleeding and reduces the chance of developing uterine cancer, in comparison to women treated with estrogen alone.

2) Before using this medicine

Do not use Progyluton if you:

- are sensitive (allergic) to the active ingredients or to any of the other ingredients contained in the medicine (see section 6 "Additional information"),
- suffer from breast cancer, or if there is a suspicion that you may have breast cancer,
- suffer from a hormone-dependent cancer such as cancer of the womb or ovaries, or if this is suspected,
- have untreated, excessive thickening of the endometrium (endometrial hyperplasia),
- have unexplained vaginal bleeding,
- have or have ever had a liver tumor (benign or malignant),
- have or have ever had a serious liver condition and the liver function values have not returned to normal,
- suffer or have ever suffered from a blood vessel disease caused by blood clotting (venous thrombosis, thrombosis, embolism),
- recently had a heart attack or stroke,
- have risk factors for the development of an arterial or venous thrombosis (blood clot) (e.g. antithrombin, protein S or protein C deficiency),
- have enhanced levels of triglycerides (a kind of blood fat),
- suffer from the metabolic disease porphyria,
- are pregnant or breastfeeding.

If any of the above events occur for the first time while you are taking Progyluton, you should stop the treatment immediately and contact your doctor.

Special warnings about using this medicine

Before using Progyluton, tell your doctor:

- if you have irregular menstruation, breast changes, breast cancer in the family or benign tumors of the womb (called myomas),
- if you have excessive thickening of the endometrium (endometrial hyperplasia) in your medical history,
- if you have or have ever had endometriosis (presence of endometrial tissue at places in the body where it is not normally found),
- if you have risk factors for blood clotting (thromboembolic diseases) (see also section entitled "Enhanced risk of developing thrombosis (blood clot)" below),
- if you suffer from migraines,
- if your blood pressure is too high,
- if you suffer from diabetes,
- if you have elevated blood lipids (hypertriglyceridemia) or if this disease has occurred in your family,
- if you suffer from a liver disease (e.g. benign liver tumor, liver adenoma) or gallbladder disease (particularly gallstones),
- if you suffer from asthma,
- if you suffer from epilepsy or involuntary movements (chorea minor),
- if you suffer from systemic lupus erythematosus (SLE; a chronic inflammatory disease),
- if you sometimes suffer or have ever suffered from persistent appearance of brown patches on your face (chloasma). In this case, you should avoid excessive exposure to the sun or ultraviolet rays;
- if you suffer from hereditary deafness (otosclerosis),
- if you suffer from hereditary angioedema (episodic swelling of body parts such as hands, feet, face or airways),
- if you suffer from a prolactinoma (a tumor) of the anterior lobe of the pituitary gland, close medical monitoring is necessary (including regular measurements of prolactin level).

In these cases, it may be necessary to have more frequent follow up tests.

Breast cancer

Several studies have reported that the risk of breast cancer is somewhat increased in women who received hormone replacement therapy for 5 years or longer. In some studies, the risk was already increased after 1 – 4 years. This risk increases during treatment with combined estrogen-progesterone agents as compared to agents containing estrogen only. The additional risk gradually decreases after hormone replacement therapy is discontinued and becomes comparable to that of women who have not received hormone replacement therapy. Of note, the additional risk may last up to 10 years after treatment in women who have received hormone replacement therapy for 5 years or longer.

Hormone replacement therapy may impair the appearance of the breast in mammograms (increases opacity in mammographic images). In certain cases, this can make it more difficult to diagnose breast cancer based on mammography. For this reason, your doctor may decide to employ other methods for follow up tests for breast cancer detection.

If you have familial history of breast cancer (e.g. in your mother or mother's sisters), you might also be at an enhanced risk of developing this disease. You should inform your doctor about this.

Endometrial cancer

If estrogens such as those contained in Progyluton are taken as monotherapy for prolonged periods, the risk of growth of the endometrium (endometrial hyperplasia) or of the development of endometrial cancer increases. The progestogen contained in Progyluton counteracts this risk.

Inform your doctor if you experience episodes of abnormal bleeding (irregular, heavy or persistent bleeding, including bloody discharge). Your doctor will investigate this using appropriate diagnostic techniques.

Ovarian cancer

Several studies suggest that hormone replacement therapy (both estrogen monotherapy and combined hormone replacement therapy) may be associated with a slightly enhanced risk of developing ovarian cancer.

Liver tumors

In rare cases, after the use of hormonal active ingredients such as those contained in Progyluton, benign liver tumors, and even more rarely malignant liver tumors have been observed, which in isolated cases led to life-threatening hemorrhages in the abdominal cavity. For this reason, the doctor has to be informed if unusual pain occurs in the upper abdomen and does not resolve soon spontaneously.

Coronary heart disease and stroke

Two major clinical trials with conjugated estrogens and medroxyprogesterone acetate (a progestogen), which are both used in hormone replacement therapy, probably indicate that the risk of heart attack is slightly increased in the first year of treatment administration. This risk was not observed when conjugated estrogens were used as monotherapy.

In two major trials evaluating these hormones, the risk of stroke was 30-40 percent higher, both when estrogens were used as monotherapy and when a combined preparation was used.

Although there is no such data for Progyluton, it should not be employed to prevent heart conditions and/or stroke.

Only limited data is available about hormone replacement therapy initiated at a relatively young age (for example, before the age of 55). This data suggests that the risk of heart attack may be lower in younger patients who have recently gone through menopause compared to older patients. However, this is not the case for strokes.

The risk of strokes is independent of age or of the time that has elapsed since menopause. The risk increases in women undergoing hormone replacement therapy as they grow older.

Enhanced risk of developing thrombosis (blood clot)

Hormone replacement therapy may increase the risk of thrombosis (a blood clot in the blood vessels).

Your doctor will check whether you are at increased risk of thrombosis, for example due to a combination of risk factors or perhaps due to one serious risk factor. In case of a combination of risk factors, the risk may be greater than the simple addition of two individual risks. If the risk is too high, your doctor will not prescribe any hormone replacement therapy for you.

The risk increases with age and may also increase

- if you or any of your close relatives suffer from thrombosis in the blood vessels of the legs or lungs;
- if you are overweight;
- if you suffer from varicose veins;
- if you are a smoker;
- if you suffer from systemic lupus erythematosus (a chronic inflammatory disease);
- if you suffer from a malignant tumor.

If you are already taking Progyluton, inform your doctor in advance of any planned hospitalization in a hospital or a surgical procedure. The risk of developing deep venous thrombosis may be temporarily increased by an operation, a serious injury, confinement to bed or restricted movement.

Dementia

During longer-term hormone replacement therapy with a different hormonal preparation, impaired memory and reduced mental function have been observed in elderly patients in very rare cases. It is not known whether the same risk exists during treatment with Progyluton.

Children and adolescents

Progyluton is not indicated for administration to children and adolescents.

Tests and follow up

Before you start taking Progyluton, you will undergo a thorough general and gynecological examination by your doctor, and he will advise you to examine your breasts by yourself and will show you how to do it.

As a precautionary measure, follow up tests should be conducted once a year when Progyluton is taken for long periods.

Estrogens may cause fluid retention (water accumulation in the tissue). Patients with heart or kidney function disorders should therefore be monitored carefully.

Drug interactions

If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist.

If taken concomitantly, certain medicines may impair the effect of Progyluton or lead to bleeding irregularities: e.g. medicines for treatment of epilepsy (barbiturates, phenytoin, carbamazepine, oxcarbazepine, topiramate, felbamate, primidone), of HIV and hepatitis C infections (protease inhibitors and non-nucleoside reverse transcriptase inhibitors), of tuberculosis (rifampicin, rifabutin), of high blood pressure in the lungs (bosentan), of a special form of excessive drowsiness (modafinil) and, if they are taken for longer periods (more than 10 days), certain antibiotics for treatment of particular infections (tetracyclines), and if St. John's wort preparations are taken (see below).

Please contact your doctor or pharmacist for advice if you must take antibiotics for a longer period (i.e. for more than 10-14 days) (e.g. for inflammation of the bones or for Lyme disease (borreliosis)).

Some medicines, as well as grapefruit juice, may increase the concentration of the active ingredient of Progyluton in the blood. Inform your doctor if you are drinking grapefruit juice or taking one of the following medicines:

- antifungals containing active substances such as itraconazole, voriconazole or fluconazole,
- certain antibiotics (known as macrolides) containing clarithromycin or erythromycin as the active substance,
- certain medicines for treatment of cardiovascular diseases (containing the active substances diltiazem or verapamil).

If you are diabetic, then your need for hypoglycemic medicines (including insulin) may be altered by taking Progyluton.

Progyluton may also influence the effect of other medicines, either by increasing or reducing their effect. This is the case, for example, for cyclosporine and the antiepileptic medicine lamotrigine (this could lead to increased frequency of seizures, which is why your doctor will monitor your lamotrigine blood level at the beginning of administration of Progyluton and after discontinuing treatment with Progyluton).

Sex hormones may also influence the effect of anticoagulants.

Tell your doctor whether you are being treated with medicines for the treatment of hepatitis C infection (medicines containing active substances such as ombitasvir, paritaprevir, ritonavir, dasabuvir, glecaprevir, pibrentasvir, sofosbuvir, velpatasvir, voxilaprevir).

It is also important that you inform your doctor or dentist that you are taking Progyluton if he prescribes new medicines for you.

Interactions with laboratory tests

Hormone replacement therapy such as Progyluton may influence certain laboratory tests. Therefore, tell your doctor or the laboratory personnel that you are taking Progyluton.

Using this medicine and food

Can be taken with or without food.

Pregnancy and breastfeeding

Progyluton must not be taken during pregnancy or during breastfeeding under any circumstances. Small amounts of sex hormones may pass into breast milk.

However, if you become pregnant during treatment with Progyluton, or if you inadvertently took this medicine during pregnancy, you must inform the doctor immediately.

You must avoid pregnancy during treatment with Progyluton. If needed, non-hormonal methods of contraception (with the exception of the calendar method according to Knaus-Ogino and the temperature measurement method) must be used. If no bleeding occurs during treatment withdrawal at regular intervals of approximately 28 days, possible pregnancy must be considered despite the use of contraceptive measures. In this situation, treatment must be discontinued, subject to investigation by the doctor.

Driving and using machines

Progyluton is not known to have any effect on the ability to drive or use machines. No specific studies have been performed in this regard. Please pay attention to undesirable effects.

Important information about some of this medicine's ingredients

Progyluton tablet contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before you start taking this medicine.

Inform your doctor or pharmacist if you:

- are suffering from other diseases,
- have allergies or
- are taking other medicines (including those you have bought yourself) or applying them externally

3) How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine. Only your doctor will determine your dose and how you should take this medicine. The recommended dosage is usually one tablet per day for 21 days. Take the tablet whole with water every day at a set hour. The time of the day at which the tablet is taken is not substantial, but you must adhere to the initially chosen time, such as after breakfast or after dinner. Do not crush/halve/chew the tablet due to the concern that the dosage will not be accurate.

The pack contains one sheet with seven self-adhesive weekday strips. In order to prepare the pack for use, you must peel off the weekday strip that starts on the day at which you start taking the tablets and attach this strip to the tablet pack at the place of "days of the week strip", so that the tablet taken on the first day is the tablet marked "1". An example: If the first day you take a tablet is Wednesday, the "days of the week" strip that starts with "We" is attached to the pack. All the remaining tablets are therefore marked with the appropriate day of the week, thus enabling you to tell at a glance whether the tablet has been taken on a particular day.

The other strips are not needed.

Start by taking the tablet that is marked by the relevant day of the week. The arrows guide you in the progress direction. Take the tablets in accordance with the direction of the arrows until the package is finished. This means that one white tablet daily should be taken for the first 11 days, then one brown tablet daily for the next 10 days. After 21 days of taking the tablets, take a 7-day break. During the 7-day break, bleeding similar to menstrual bleeding may occur; this is normal. Start taking tablets from the next package on the eighth day, even if the bleeding continues. In this way, you will start a new package each month on the same day of the week.

When can you start taking the medicine for the first time?

- If you have regular periods, start taking the medicine on the fifth day of the period.
- If you do not have regular periods, you can start taking the medicine at any time that you choose.
- If you are taking another hormone replacement therapy that causes you to have a period, complete the treatment course as required and start taking Progyluton on the next day.
- If you are taking another hormone replacement therapy that does not cause you to have a period, you can start taking Progyluton at any time that you choose.

Do not exceed the recommended dose.

Treatment duration

Your doctor will determine - according to your needs - how long you should take Progyluton.

If you have accidentally taken a higher dose

There have been no reports of overdose. However, headaches, nausea, vomiting, feeling of tightness in the breasts and bleeding in the womb may occur. No special treatment is needed, but you should see your doctor.

If a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the tablet:

- If the delay in taking the tablet is less than 12 hours, take the tablet as soon as possible, and continue taking the rest of the tablets as usual, in the direction of the arrow and at your regular time.
- If the delay in taking the tablet is more than 12 hours, leave the forgotten tablet in the package and continue taking the rest of the tablets as usual, in the direction of the arrow, at your regular time.
- Bleeding may occur if you have missed a tablet. This is normal.

Adhere to the treatment as recommended by your doctor.

Even if your health improves, do not stop taking this medicine without consulting your doctor.

Do not take medicines in the dark! Check the label and dose every time you take a medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4) Side effects

Like with all medicines, using Progyluton may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Serious side effects

Stop using the medicine immediately in the following cases:

- first onset of migraine-like headaches or more frequent occurrence of unusually severe headaches,
- sudden impairment of perception (e.g. vision disorders, hearing disorders),
- first signs of venous inflammation accompanied by thrombosis or of conditions resulting from blood clots (embolism) (e.g. unusual leg pain or leg swelling, sharp pain when breathing or cough without apparent cause, fainting),
- pain and feeling of tightness in the chest area,
- jaundice,
- hepatitis,
- itching over the entire body,
- growth of myomas (benign tumors of the womb),
- increased epileptic seizures,
- sharp increase in blood pressure,
- pregnancy.

Additional side effects

Very common (affect more than one in 10 users)

Feeling of tightness in the breasts, breast pain, bleeding irregularities (menorrhagia, metrorrhagia, spotting, etc.)

Common (affect 1 to 10 in 100 users)

Weight gain, mood swings, depression, headache, flatulence, stomach pain, nausea, excess stomach acid, skin rashes, itching, back pain, lower abdominal pain, increased vaginal discharge, enlargement of uterine myomas (benign tumor of the womb), enlargement of the breasts, edema (water retention), weakness or asthenia.

Uncommon (affect 1 to 10 in 1,000 users)

Breast cancer, hypersensitivity reactions, altered sex drive, nervousness, sleep disorders, dizziness, migraine, vision impairment, palpitations, blood pressure elevation, arterial or venous thrombosis (blood clots), vomiting, abnormal liver function values, acne, excessive hair growth (hirsutism), hair loss, hives (urticaria), muscle cramps.

Rare (affect 1 to 10 in 10,000 users)

Anxiety, painful menstruation, premenstrual syndrome.

Very rare (affect less than 1 in 10,000 users)

Jaundice

Other undesirable effects have been reported by women using hormone replacement therapy, but the relationship with Progyluton has been neither confirmed nor refuted.

Endometrial cancer, weight loss, gallstones (and other gallbladder diseases), brown patches on the face (chloasma), inflammatory skin changes with reddish papules (erythema nodosum), inflammatory skin changes with or without blistering (erythema multiforme), ruptured veins under the skin (vascular purpura), enlargement of the endometrium (endometrial hyperplasia).

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link:

https://sideeffects.health.gov.il

5) How to store the medicine?

Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.

Do not use the medicine after the expiry date (exp. date) which is stated on the package/blister. The expiry date refers to the last day of that month.

Storage conditions

Do not store at a temperature above 25°C.

6) Additional information

In addition to the active ingredient(s), this medicine also contains:

White tablets

lactose monohydrate, maize starch, povidone 25, talc, magnesium stearate.

Tablet coating:

sucrose, calcium carbonate, talc, macrogol 6000, povidone 90, glycol montanate.

Light brown tablets

lactose monohydrate, maize starch, povidone 25, talc, magnesium stearate.

Tablet coating:

sucrose, calcium carbonate, talc, macrogol 6000, titanium dioxide povidone 90, glycerol 85%, ferric oxide red, ferric oxide yellow, glycol montanate.

What the medicine looks like and contents of the pack:

In a Progyluton package, there are 10 light brown tablets and 11 white tablets.

Each package contains 21 tablets packed in blisters.

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

Manufacturer's name and address: Bayer Weimar GmbH und Co. KG, Weimar, Germany.

Revised in May 2022 according to the Ministry of Health guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 032 90 22502 00