Information for patients

Progyluton - coated tablets

estradiol valerate/norgestrel

Read this package insert carefully before taking or using the drug.

- This drug was prescribed for you personally and you should not pass it on to other persons. Even if they have the same symptoms as you, the drug might harm them.
- Keep the package leaflet, because you might want to read it again later.

WHAT IS PROGYLUTON AND WHEN IS IT USED?

Progyluton belongs to a type of treatment called hormone replacement therapy (HRT). It contains two female sex hormones known as estradiol (an estrogen) and norgestrel (a progestogen). The active ingredient estradiol is equivalent to the natural hormone and possesses the same properties, whereas norgestrel has an effect similar to that of the natural corpus luteum hormone progesterone.

In the fertile years of a woman estrogens and progestogens are produced by the ovaries. They regulate the monthly cycle and the normal course of a pregnancy. In the menopause (change of life), which is a natural process and occurs in every woman, the ovaries cease producing these hormones, usually between the ages of 45 and 55, but also for example in younger women whose ovaries have been surgically removed or inactivated by irradiation.

In many women the discontinuation of estrogen production in the menopause leads to typical complaints. In particular these include hot flashes, tendency to have outbreaks of sweating, sleep disturbances, depressive moods, nervous irritability, headache, dizziness, as well as retrogression of the mucous membranes in the area of urinary and sex organs. These disturbances can be alleviated or removed by replacing the hormone that is no longer produced in the body. The composition and effect of Progyluton is tuned in such a way that when taken regularly a cyclical pattern ensues that corresponds to the normal cycle.

Depressive moods, however, are only favorably influenced by Progyluton when they occur in conjunction with hot flashes.

Other applications are missing or missed periods resulting from hormonal disturbances, and too frequent, too rare or irregular menstruation.

The active ingredient estradiol induces the growth of the mucous lining of the womb (endometrium). This inducement of uterine mucous membrane growth can sometimes lead to irregular bleeding and in some cases to an undesired proliferation of the endometrium called endometrial hyperplasia. Owing to the progestogen contained in Progyluton the risk of endometrial hyperplasia is reduced by the periodic bleeding during which the endometrium is regularly shed, thus protecting the womb. For this reason Progyluton is only employed in women with an intact womb.

Progyluton is used during the change of life (perimenopause).

Progyluton may only be used on prescription and under constant supervision by a doctor.

WHAT NEEDS TO BE TAKEN INTO ACCOUNT HERE?

Progyluton is not a contraceptive (see «When is caution needed when taking Progyluton?»).

HRT may be associated with a higher risk of contracting certain diseases such as breast cancer, cardiovascular diseases (heart attack, stroke, venous thrombosis and pulmonary embolisms - development of blood clots in vessels) (see «When is caution needed when taking Progyluton?»). Your doctor will weigh up the risks of hormone therapy compared with the expected benefits and will discuss this with you.

WHEN MUST PROGYLUTON NOT BE USED?

Progyluton must not be used if you:

- are suffering from breast cancer, or if there is a suspicion that you may have breast cancer,
- are suffering from a hormone-dependent tumor 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 once had a liver tumor (benign or malignant),
- have or once had a serious liver condition and the liver function values have not returned to normal,
- are suffering or once suffered from a blood vessel disease caused by blood clotting (venous thrombosis, thrombosis, embolism),
- recently had a heart attack or stroke,
- possess 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,
- are hypersensitive (allergic) to any of the constituents of Progyluton.

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

WHEN IS CAUTION NEEDED WHEN TAKING PROGYLUTON?

Before any Progyluton treatment your doctor will discuss the risks and benefits of treatment with Progyluton.

Before starting to take Progyluton you will be given a thorough general and gynecological checkup by your doctor, and he or she will advise you to examine your breasts on your own and will show you how to do it.

As a precautionary measure checkups should be conducted once a year when Progyluton is taken for long periods.

During treatment with Progyluton pregnancy must not occur (see «May Progyluton be taken during pregnancy or lactation?»). If needed, non-hormonal methods of contraception (with the exception of the calendar method according to Knaus-Ogino and the temperature method) must be used. If during treatment withdrawal bleeding fails to occur at regular intervals of approx. 28 days, pregnancy must be considered a possibility despite the contraceptive measures. Treatment must then be discontinued pending clarification by the doctor.

Reasons for immediate discontinuation of Progyluton treatment are:

- 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 with thrombosis or of conditions resulting from blood clots (embolism) (e.g. unusual leg pain or leg swelling, sharp pains when breathing or a 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.

Reasons for more frequent medical checkups:
It is important that you should inform your doctor if you are suffering or have at any time suffered any of the following disorders. In these cases it may be necessary to have checkups at closer intervals:

- if you have irregular menstruation, breast changes, breast cancer in the family or benign tumors of the womb (so-called myomas),
- if you have excessive thickening of the endometrium (endometrial hyperplasia) in your medical history,
- if you have or once 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 for development of 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 St. Vitus' dance (chorea minor),
- if you suffer from systemic lupus erythematosus (SLE; a chronic inflammatory disease),
- if persistent brown patches sometimes appear or have appeared on your face (chloasma). In this case, you should not expose yourself too much 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 the prolactin level).

Breast cancer
Various scientific studies have reported that the risk of breast cancer is slightly increased in women who use hormone replacement therapy for longer than 5 years. In some studies, the risk was already increased after 1 – 4 years of use. In general, the increased risk was higher with combined estrogen-progestogen therapy than with estrogen-only therapy. This risk slowly decreases after hormone replacement is discontinued and is then again comparable to that of women who have not used hormone replacement therapy. However, the risk may last 10 years or longer if you have used HRT for more than 5 years.

HRT 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 from mammography. For this reason your doctor may decide to employ other methods for breast cancer checkups.

If breast cancer has occurred in your family's past (e.g. in your mother or mother's sisters), there might be an enhanced risk of this disease occurring in you, too. You should inform your doctor about this.

Endometrial cancer
If estrogens such as those in Progyluton are taken by themselves for prolonged periods, the risk of growth of the endometrium (endometrial hyperplasia) or of the development of endometrial cancer will rise. The progestogen in Progyluton counteracts this risk.

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

Ovarian cancer
Several studies suggest that HRT (both for estrogen single-drug therapy and also for combined HRT) could 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 that are 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 is to be informed if unusual pain occurs in the upper abdomen and does not disappear soon of its own accord.

Coronary heart disease and stroke
Two major clinical trials with conjugated estrogens and medroxyprogesterone acetate (a progestogen), which are both used in HRT, seem to indicate that the risk of suffering a heart attack may be slightly higher in the first year of administration. This risk was not observed when conjugated estrogens were used on their own.

In two major trials involving these hormones the risk of suffering a stroke was 30-40 per cent higher, both when estrogens were used alone and when a combined preparation was used.

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

Only limited data is available about HRT initiated at a relatively early age (for example, before the age of 55). This data suggests that the risk of heart attack could be lower in younger patients who have gone through menopause more recently than in 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 HRT as they grow older.

Enhanced risk of developing a thrombosis (blood clot)
HRT may increase the risk of thrombosis (blood clot in the 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 very serious risk factor. In the 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 has had a 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 are suffering from a malignant tumor disease.

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

Dementia
During longer-term HRT with a different hormonal preparation, impaired memory and reduced mental performance have been observed in elderly patients in very rare cases. It is not known whether the same risk exists with Progyluton.

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

Each Progyluton coated tablet contains approximately 46 mg lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are following a lactose-free diet should bear in mind this quantity.

Interactions with laboratory tests
An HRT such as Progyluton may influence certain laboratory investigations. Therefore, tell your doctor or the laboratory personnel that you are taking Progyluton.

Interactions with other medicinal products
If taken concomitantly, certain medicinal products may impair the effect of Progyluton or lead to bleeding irregularities: e.g. medicinal products 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 ask your doctor or pharmacist about what to do next 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 borreliosis).

Some medicinal products as well as grapefruit juice may increase the concentration of the active substance of Progyluton in the blood. Inform your doctor if you are taking one of the following medicinal products or grapefruit juice:

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

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

Progyluton may also influence the effect of other medicinal products, either by increasing or reducing their effect. This is the case, for example, for ciclosporin and the antiepileptic 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 when you discontinue Progyluton).

Sex hormones may also influence the effect of anticoagulants.

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

Tell your doctor or pharmacist if you:

- suffer from other illnesses,
- have any allergies or
- are taking or outwardly applying any other medicines (including those bought over the counter)

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

Effect on ability to drive and use 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 take note of the undesirable effects.

MAY PROGYLUTON BE TAKEN DURING PREGNANCY OR DURING LACTATION?

Progyluton must not be taken during pregnancy or during lactation under any circumstances. Small amounts of sex hormones may pass into the mother's milk. During pregnancy and lactation there is no medical indication for this medicinal product either.

Should you nevertheless become pregnant during the Progyluton treatment, or if you inadvertently took this drug during pregnancy, you must inform the doctor immediately.

HOW DO YOU USE PROGYLUTON?

How and when should Progyluton be taken?
If at present you are not using or taking any other preparation for hormone replacement therapy and are still having your periods, you should start treatment on the fifth day of the cycle (first day of menstruation = day one of the cycle). If you no longer have any periods you can start on Progyluton straight away.

If you are already using or taking another preparation, start the therapy with Progyluton on the day after discontinuing therapy with the other preparation or as your doctor advises.

The pack also contains one or three sheets, each with seven self-adhesive weekday strips. In order to prepare the pack for use you must peel off that strip that on the left shows the day of the week the coated tablets are started and stick this strip on the coated tablet pack where "days of the week strip" stands to make the day the first coated tablet is taken align with the tablet marked "1". An example: If the first day you take a coated tablet is a Wednesday, the "days of the week" strip that starts on the left with "We" is stuck on the pack. All the remaining coated tablets are thus marked with the appropriate day of the week, therefore enabling one to tell at a glance whether the day's coated tablet has been taken.

The other strips are not needed.

Tablet-taking always starts with the well marked "Start" and continues in the direction of the arrows until all the 21 coated tablets have been taken. The coated tablets are to be swallowed whole with some liquid.

After the 21 days of treatment take a break of seven days, during which menstruation-like withdrawal bleeding occurs - roughly 2-4 days after the last coated tablet was taken. Unless prescribed otherwise by the doctor start a new pack after the seven-day break on the same day the previous one was started.

The time of day the tablet-taking occurs is immaterial, but one should always stick to the time initially selected, e.g. after breakfast or after the evening meal.

What should one do if one has forgotten to take Progyluton?
If you forget to take the coated tablet at the usual time of day, take it as soon as you noticed that you forgot it, and take the next tablet at the usual time of day. If more than 24 hours have elapsed, you should leave the missed tablet in the blister pack. Continue taking the remaining coated tablets at the customary time of day.

If several tablets are missed there may be irregular bleeding.

What should one do if one took too many Progyluton tablets?
There have been no reports of overdosage. However, it is possible for headaches, nausea, vomiting, feeling of tightness in the breasts and bleeding in the womb to occur. No special treatment is needed, but you should see your doctor.

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

Do not change the prescribed dosage on your own. If you think that the drug is too weak or strong in its effect, talk to your doctor or pharmacist.

Special dosage instructions
Children and adolescents

Progyluton is not indicated for administration to children and adolescents

Elderly patients

There are no data to suggest that it is necessary to adjust the dosage for elderly patients.

Impaired liver function

Progyluton has not been specially investigated in patients with impaired liver function. Progyluton must not be used by women with severe liver disorders (see: "When must Progyluton not be used?").

Impaired kidney function

Progyluton has not been specifically investigated in patients with impaired kidney function. Therefore, no dosage recommendations can be made.

Do not deviate from the prescribed dosage. If you believe that the effect of the medicine is too weak or too strong, talk to your doctor or pharmacist.

WHAT SIDE EFFECTS CAN PROGYLUTON HAVE?

The serious side effects that can occur in association with HRT are described in the section above entitled "When is caution needed when taking Progyluton?". Please read that section for further information.

Other side effects reported by women on HRT which can be neither corroborated nor ruled out in connection with Progyluton are:

Very common (affects more than 1 in 10 treated patients)
Feeling of tightness in the breasts, breast pain, bleeding irregularities (menorrhagia, metrorrhagia, spotting, etc.)

Common (affects 1 to 10 in 100 treated patients)
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 (affects 1 to 10 in 1,000 treated patients)
Breast cancer, hypersensitivity reactions, altered sex drive, nervousness, sleep disorders, dizziness, migraine, visual impairment, palpitation, 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 (affects 1 to 10 in 10,000 treated patients)
Anxiety, painful menstruation, premenstrual syndrome.

Very rare (affects less than 1 in 10,000 treated patients)
Jaundice

Other undesirable effects have been reported by HRT users, 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 get any side effects, talk to your doctor, pharmacist. This particularly includes any possible side effects not listed in this leaflet.

<table>
<tr><td colspan="2">To report any side effect(s):</td></tr>
<tr><td>Oman:
Tel: +968 - 2444 1999
Fax: +968 - 24602287
Email: pharma-vigil@moh.gov.om
Website: www.moh.gov.om</td><td>Jordan:
Tel: +962-6-5632000
JFDA email : jpc@jfda.jo
JFDA website: www.jfda.jo
http://primaryreporting.who-umc.org/JO</td></tr>
<tr><td rowspan="2">United Arab Emirates (UAE):
Pharmacovigilance & Medical Device section
Tel: 80011111 / +971 42301000
Email: pv@mohap.gov.ae
Website: www.mohap.gov.ae
P.O.Box 1853 Dubai</td><td>Kuwait:
Hotline: 1810005
Email: health@moh.gov.kw
Website: www.moh.gov.kw/kdfc/
P.O.Box: 5 Safat, 13001 Kuwait</td></tr>
<tr><td>Other Countries:
Please contact the relevant competent authority</td></tr>
</table>

WHAT ELSE MUST BE BORNE IN MIND?

Keep out of the reach and sight of children.

The medicinal product may only be used up to the «EXP» date shown on the container.

Do not store above 30°C.

Your doctor or pharmacist can give your further information. These persons have the more detailed professional datasheet at their disposal.

WHAT DOES PROGYLUTON CONTAIN?

Active ingredients:

- White coated tablets: 2 mg estradiol valerate
- Light brown coated tablets: 2 mg estradiol valerate and 0.5 mg norgestrel.

Excipients

- White coated tablets: 46.2 mg lactose monohydrate, maize starch, povidone K25, magnesium stearate, talc, 34.0 mg sucrose, povidone K90, macrogol 6000, calcium carbonate, glycol montanate.
- Light brown coated tablets: 45.7 mg lactose monohydrate, maize starch, povidone K25, magnesium stearate, talc, 33.4 mg sucrose, povidone K90, macrogol 6000, calcium carbonate, glycerol (E422) 85%, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), glycol montanate.

WHERE DO YOU OBTAIN PROGYLUTON?

WHAT PACKS ARE AVAILABLE?

You can only obtain Progyluton in pharmacies on medical prescription.

There are calendar packs containing 1 x 21 coated tablets and 3 x 21 coated tablets.

Not all pack sized may be marketed.

Manufacturer
Bayer Weimar GmbH and Co. KG
Dobereinerstrasse 20,
99427 Weimar, Germany.

Marketing authorisation holder
Bayer AG
Kaiser-Wilhelm-Allee 1
51368 Leverkusen, Germany.

This package insert was last checked by the drug authority (Swissmedic) in January 2022.

This is a medicament

- A medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists0