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Progyluton®

Composition

Active substances

Estradiol valerate, norgestrel.

Excipients

White sugar-coated tablets: 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.

Pharmaceutical form and active substance quantity per unit

A blister of 11 white and 10 light brown coated tablets (sugar-coated tablets) contains per sugar-coated tablets:

white: estradiol valerate 2 mg.

light brown: estradiol valerate 2 mg, norgestrel 0.5 mg.

Indications/Uses

Perimenopausal syndrome in patients with an intact uterus, primary and secondary amenorrhoea, abnormal menstrual rhythms, deficiencies following oophorectomy or radiation castration due to non-cancerous diseases in nonhysterectomized patients.

Dosage/Administration

Treatment initiation: 1 sugar-coated tablet daily from the 5^{th}–25^{th} day of the cycle (1^{st} day of menstruation = 1^{st} day of the cycle). This is followed by 7 tablet-free days during which menstrual-like bleeding occurs a few days after the last sugar-coated tablet has been taken.
Treatment continuation: Starts after each 7-day tablet-free interval. Administration of each new pack is thus always started on the same day of the week.

Patients with amenorrhoea or very irregular bleeding can take Progyluton immediately after pregnancy has been ruled out. Treatment is started with 1 white sugar-coated tablet daily for 11 days, followed by 1 light brown sugar-coated tablet daily for 10 days.
The sugar-coated tablets are swallowed whole with liquid. The sugar-coated tablets should preferably be taken at the same time every day.
The lowest effective dose should always be used for the shortest possible duration of treatment for all indications. Hormone replacement should only be continued if the benefits outweigh the risks for the individual patient.

Forgotten doses

If a sugar-coated tablet is forgotten at the usual time, it should be taken as soon as possible. If more than 24 hours have elapsed, no additional sugar-coated tablets must be taken. Irregular bleeding may occur if several sugar-coated tablets have been forgotten.

Absence of withdrawal bleeding

If, in exceptional cases, no withdrawal bleeding occurs, pregnancy must be ruled out before continuation of treatment.

Intermenstrual bleeding

In women during and especially after perimenopause, all forms of intermenstrual bleeding must be diagnostically clarified.
If intermenstrual bleeding occurs in younger women, Progyluton administration must be continued.
If breakthrough bleeding does not stop or if it recurs, a appropriate examination including curettage is indicated to rule out an organic cause.
The same applies to spotting that occurs for several cycles in succession at irregular intervals or for the first time after prolonged use of Progyluton.

Special dosage instructions

Elderly patients

There are no data indicating that a dose adjustment is necessary in elderly patients.

Children and adolescents

No data are available on the safety and efficacy of Progyluton in children and adolescents under 18 years of age. There is no indication in this age group.

Patients with hepatic disorders

Progyluton has not been investigated in patients with hepatic disorders. Progyluton is contraindicated in patients with severe hepatic impairment. No dose adjustment is required in patients with mild to

moderate hepatic impairment. However, patients should be monitored closely (see "Warnings and Precautions").

Patients with renal disorders

Progyluton has not been investigated in patients with renal disorders. Therefore, no dosage recommendations can be made.

Contraindications

Existing or suspected breast cancer,

- Existing or suspected sex hormone-dependent premalignancy or malignancy
- Untreated endometrial hyperplasia,
- Undiagnosed vaginal bleeding,
- Previous or existing benign or malignant liver tumours,
- Severe liver disease (including history thereof), until liver function values have returned to normal,
- Previous or existing venous thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism),
- Acute or recent arterial thromboembolic events (cerebral infarction, myocardial infarction),
- Risk factors for arterial or venous thromboembolic events (e.g., antithrombin, protein S or protein C deficiency),
- Severe hypertriglyceridaemia,
- Porphyria,
- Pregnancy and breast-feeding,
- Known hypersensitivity to any of the ingredients of Progyluton.

Warnings and precautions

All hormone replacement therapy (HRT) should be preceded by an examination of the general clinical condition and a thorough gynaecological examination, which must be repeated at least once a year. The personal and family medical history should also be taken into consideration. The risk-benefit ratio must be carefully assessed for each patient before start of treatment and should also be reviewed on a regular basis during treatment. The lowest effective dose should always be used for the shortest possible duration of treatment.

Reasons for immediate withdrawal of therapy

If one of the contraindications mentioned above occurs during HRT or if one of the following situations occurs, treatment must be discontinued immediately:

- Symptoms of a venous or arterial thromboembolic event or suspicion thereof, including:
    - Migraine-like headache occurring for the first time or more frequent occurrence of unusually severe headache

  - Sudden partial or complete loss of vision
  - Sudden hearing disorders
- Clinically relevant blood pressure increase
- Deterioration of hepatic function or occurrence of jaundice or hepatitis
- Detectable growth of myomas
- Increase in epileptic seizures
- Pregnancy

Situations that require particular monitoring

If the following symptoms occur, have recently occurred and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be carefully monitored. It should be borne in mind that these symptoms may recur or worsen during treatment with Progyluton:

- Risk factors for oestrogen-dependent tumours (e.g., breast cancer in a first-degree relative)
- Benign breast changes
- Endometrial hyperplasia (including history thereof)
- Leiomyoma or endometriosis
- Risk factors for thromboembolic disorders (see also “Thromboembolic diseases” section)
- Migraine
- Hypertension
- Diabetes mellitus
- Hypertriglyceridaemia
- Diseases of the liver or gallbladder
- Asthma
- Epilepsy
- Systemic lupus erythematosus
- Chorea minor
- Otosclerosis

In the event of deterioration or first-time occurrence of the following conditions or risk factors, the individual risk-benefit analysis should be reviewed and, if applicable, treatment discontinued.

Tumours

Breast cancer

Randomised controlled studies and epidemiological studies showed an increased risk of breast cancer in women who used HRT for several years. The risk is particularly increased with a use period of more than 5 years. In a meta-analysis of epidemiological studies, the relative risk in women who used HRT for 5 or more years was 1.35 (95% CI 1.21-1.49). In individual studies, however, an

increase in risk was also observed after a shorter duration of therapy (1-4 years). In general, the risk increase was higher with combined estrogen-progestin therapy than with estrogen monotherapy.
All women should therefore undergo breast examinations by a physician before HRT is initiated and on a yearly basis and should carry out self-examinations of the breasts on a monthly basis. Depending on age and the respective risk factors, a mammogram may also be indicated. Users should be advised what changes in their breasts they need to report to their physician.
Two large meta-analyses of epidemiological studies showed that the risk of developing breast cancer increases in proportion to the duration of HRT and decreases after discontinuation of HRT. The time to return to age-appropriate risk baseline dependeds on the duration of previous HRT use. If the duration of use exceeds 5 years, the risk may still be increased for 10 years or more after discontinuation.
The Women's Health Initiative (WHI) study, a large, prospective, placebo-controlled, randomised study, showed an increase in invasive breast cancer in the oestrogen/progestogen group (RR 1.24 [95% CI 1.02–1.50]) in more than 8,000 elderly, postmenopausal women (age at start of study 50–79 years, mean age 63 years) compared to placebo under combined HRT with conjugated oestrogens and medroxyprogesterone acetate (MPA) after an average treatment duration of 5.6 years. However, the risk with oestrogen monotherapy was not increased (RR 0.77 [95% CI 0.59–1.01]).
The Million Women Study, a non-randomised cohort study, recruited 1,084,110 women. The average age of the women upon enrolment in the study was 55.9 years. Half of the women received HRT before and/or at the time of starting the study while the other women were never treated with HRT. 9,364 cases of invasive breast cancer and 637 deaths due to breast cancer were recorded following an average observation time of 2.6 and 4.1 years, respectively. Women who used HRT upon enrolment in the study showed a higher risk in terms of morbidity (RR 1.66 [95% CI 1.58–1.75]) and possibly, to a lesser extent, mortality due to breast cancer (RR 1.22 [95% CI 1.00–1.48]) compared with the women who had never received such treatment. The highest risk was observed with combined oestrogen-progestogen therapy (RR 2.00 [95% CI 1.88–2.12]). The relative risk for oestrogen monotherapy was 1.30 (95% CI 1.21–1.40). The results were similar for various oestrogens and progestogens, for various doses and administration routes as well as for continuous and sequential therapies. The risk increased in proportion to the duration of administration for all types of HRT.
HRT increases the density of mammographic images, which may impair radiological detection of breast cancer in some cases.

Endometrial cancer

Prolonged intake of oestrogens increases the risk of developing endometrial hyperplasia or endometrial carcinoma. Studies indicate that this risk increase is largely reduced by administering an additional progestogen.

Medical supervision of all women who use HRT is necessary. All cases of abnormal bleeding (irregular, heavy or persisting bleeding, including spotting) must be clarified using suitable diagnostic measures (including histological examination of the endometrium if applicable) to rule out an organic cause or malignancy.

Ovarian cancer

Several epidemiological studies indicate that HRT could be associated with an increased risk of developing epithelial ovarian cancer. A risk increase was detected with both oestrogen monotherapy and combined HRT. While most studies showed a risk increase only with long-time use (i.e. at least 5 years), a meta-analysis published in 2015 (evaluating a total of 17 prospective and 35 retrospective studies) did not reveal a correlation with duration of administration.
In the prospective, randomised, placebo-controlled WHI study, there was no statistically significant risk increase (HR 1.41; 95% CI 0.75–2.66).
Since ovarian cancer is much rarer than breast cancer, the absolute risk increase in women who use or have recently used HRT is low.

Liver tumours

In rare cases, benign and, even more rarely, malignant liver changes have been observed following use of hormonal active substances, such as those contained in Progyluton, leading to life-threatening intra-abdominal haemorrhage in isolated cases. If severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnostic considerations.

Coronary heart disease and stroke

HRT should not be used to prevent cardiovascular disease.
Large clinical studies showed no favourable effect in the primary prophylaxis (WHI study) or secondary prophylaxis (HERS study) of cardiovascular disease.
The WHI study showed an increased risk of cardiovascular events compared to placebo in postmenopausal women who had received oral HRT with conjugated oestrogens and MPA for an average of 5.2 years (RR 1.24 [95% CI 1.00–1.54], absolute risk increase of 6 cases per 10,000 person-years). The risk was highest in the first year after initiation of HRT (RR 1.81 [95% CI 1.09-3.01]). The risk increased in proportion to the time since menopause (menopause < 10 years: RR 0.89; menopause 10–19 years: RR 1.22; menopause ≥ 20 years: RR 1.71).
The cerebrovascular risk under combined oestrogen-progestogen therapy was also increased in the WHI study (RR 1.31 [95% CI 1.02–1.68]).
No significant influence on the cardiovascular risk could be found in the oestrogen monotherapy arm of the WHI study (RR 0.91 [95% CI 0.75–1.12]). However, the risk of cerebrovascular accidents was increased (RR 1.39 [95% CI 1.10–1.77]).

The Heart and Estrogen/Progestin Replacement Study (HERS and HERS II), a prospective, placebo-controlled, randomised study, showed no reduction in cardiovascular risk in more than 1,300 postmenopausal women with pre-existing coronary artery disease (mean age at study enrolment 67 years) who had received oral HRT with conjugated oestrogens and MPA for an average of 4.1 years (HERS) and 2.7 years (HERS II). The relative risk was 0.99 (95% CI 0.84–1.17). The risk was highest in the first year after initiation of HRT (RR 1.52 [95% CI 1.01–2.29]).
Only limited data are available on HRT with start of treatment at a relatively early age (for example, before 55 years of age). These indicate that the increase in cardiovascular risk under HRT in younger patients with a short time since menopause could be less than in the (usually older) population investigated in the aforementioned studies. However, this does not apply to cerebrovascular events. The relative risk of cerebrovascular accidents does not depend on age or time since menopause. As the baseline risk of stroke is strongly age-dependent, however, the overall risk in women who use HRT rises with increasing age.
Alternative therapies should be considered for women who already have risk factors for cardiovascular or cerebrovascular events.

Venous thromboembolism (VTE)

HRT is associated with an increased risk of VTE (e.g. deep vein thrombosis, pulmonary embolism). Two controlled randomised studies (HERS and WHI) and several epidemiological studies showed a 2–3-fold risk increase in women who used HRT compared to women who had never received such therapy. The WHI study showed an increased incidence of pulmonary embolisms in particular. The absolute risk increase in the women treated with HRT was 8 cases per 10,000 person-years (15 vs 7) and the relative risk was 2.13 (95% CI 1.39–3.25).
The increased risk was only found in women undergoing HRT and not in women who had previously used HRT. The risk seems to be higher in the first few years of use.
The risk of venous thromboembolism also tended to be higher in the oestrogen monotherapy arm of the WHI study. The relative risk of deep vein thrombosis was 1.47 (95% CI 0.87–2.47), while that of pulmonary embolism was 1.34 (95% CI 0.70–2.55).
For non-users, the number of VTE cases for a period of 5 years is estimated at 3 in 1,000 women for the age group 50–59 years and at 8 in 1,000 women for the age group 60–69 years. In healthy women who receive HRT for 5 years, there are an additional 2–6 cases per 1,000 women in the age group 50–59 years and an additional 5–15 cases in the age group 60–69 years.
The preparation must be discontinued immediately if corresponding symptoms occur or a VTE is suspected. Patients with risk factors for thromboembolic events should be carefully monitored. For these women, the risk-benefit ratio must be carefully assessed and, if possible, other therapies considered.

The known risk factors for VTE include corresponding personal or family medical history (occurrence of VTE in a close relative at a relatively early age can indicate a genetic predisposition), smoking, significant obesity, systemic lupus erythematosus and malignancies.
In women who have a combination of risk factors or a higher degree of severity for a single risk factor, it should be taken into account that the risk may be excessively increased. This may result in a contraindication for HRT under certain circumstances.
The risk of venous thromboembolic events may be temporarily increased in the event of prolonged immobilisation, major surgery or after major trauma. In women receiving hormone replacement, prophylactic measures are of utmost importance in order to avoid venous thromboembolism after surgery. Depending on the type of surgery and duration of immobilisation, temporary suspension of HRT should be considered; in case of elective surgeries, this should be several weeks (4–6 weeks) before surgery if possible. Treatment should not be resumed until the woman is completely mobilised.

Dementia

In the Women's Health Initiative Memory Study (WHIMS), a randomised, placebo-controlled study subordinate to the WHI study, more than 2,000 women aged > 65 years (average age 71 years) were treated with oral conjugated equine oestrogens and medroxyprogesterone acetate with an average follow-up of 4 years.
In addition, 1,464 hysterectomised women aged 65 to 79 years were treated with oral conjugated equine oestrogens only with an average follow-up of 5.2 years. Neither treatment with conjugated oestrogens and medroxyprogesterone acetate nor oestrogen monotherapy showed a favourable effect on cognitive function. The risk of cognitive function disorders (probable dementia) was even increased for combined HRT (RR 2.05 [95% CI 1.21–3.48]). In absolute numbers, this means 23 additional cases per 10,000 treated women per year.
Although it is unclear to what extent these results can be extrapolated to a younger population or to HRT preparations with other active substances, they should be taken into account by the physician when assessing the risk-benefit ratio of HRT.

Other precautions

Oestrogens can cause fluid retention. Patients with diseases that can deteriorate as a result of this (such as cardiac or renal dysfunction, asthma, epilepsy or migraine) should therefore be carefully monitored.
A definitive connection between HRT use and the occurrence of clinical hypertension has not been documented to date. A slight increase in blood pressure has been observed in women under HRT; however, a clinically relevant increase is rare. If persistently increased blood pressure values occur during HRT, discontinuation of HRT should be considered.
Blood pressure should be monitored regularly in patients who take blood pressure lowering medicinal products concomitantly with Progyluton.

HRT can result in increased triglyceride levels, which can increase the risk of pancreatitis in patients with pre-existing hypertriglyceridaemia. Triglyceride levels should therefore be monitored in these patients.
Clinical studies showed an effect of HRT on peripheral insulin resistance and glucose tolerance. However, it is generally not necessary to adjust antidiabetic treatment. Blood glucose levels should be monitored carefully in diabetic patients receiving HRT.
Women with hepatic function disorders, including hyperbilirubinaemia such as Dubin-Johnson syndrome or rotor syndrome, must be monitored carefully and the liver parameters must also be monitored. If liver values deteriorate, HRT should be discontinued.
Oestrogens may increase the lithogenicity of bile. Several epidemiological studies found a small but statistically significant increase in the risk of gallbladder diseases (especially cholelithiasis) or an increased incidence of cholecystectomy during HRT. This should be considered especially in patients with additional risk factors for cholelithiasis (e.g., obesity, hyperlipidemia).
Patients with a pre-existing prolactinoma require close medical monitoring (including regular prolactin level tests), since increases in the size of prolactinomas during oestrogen therapy have been reported in isolated cases.
As with all preparations containing oestrogen, Progyluton should only be used after careful assessment of the risks and benefits in patients with renal impairment or with metabolic bone diseases accompanied by hypercalcaemia.
During HRT, undesirable effects, such as unusually heavy bleeding, can occur in some patients due to oestrogen stimulation. Frequent and persistent irregular bleeding is a sign of endometrial activity and must be clarified by suitable diagnostic measures to rule out organic diseases.
Uterine myomas may increase in size under oestrogen treatment. If this is observed, treatment should be discontinued.
If endometriosis is reactivated under HRT, discontinuation of therapy is recommended.
Exogenous estrogen supply leads to an increase in serum concentrations of thyroxine-binding globulin (TBG). In women with normal thyroid function, this is of no clinical relevance. Studies suggest that in patients undergoing thyroid hormone replacement therapy, the additional administration of an estrogen preparation (such as Progyluton) could lead to increased thyroxine requirements. Patients on thyroid hormone replacement therapy should therefore have their thyroid function monitored regularly (by TSH determination), especially during the first months of HRT.Chloasma may occur occasionally, especially in women with a history of chloasma gravidarum. Women prone to chloasma should avoid exposure to the sun or other ultraviolet radiation during HRT.
In women with hereditary angioedema, exogenously administered oestrogens may induce or exacerbate symptoms of angioedema.
The risks of HRT reported above have been described predominantly in women over the age of 50 years. No experience is available on the transferability of these data to patients with premature

menopause (i.e., failure of ovarian function before 40 due to endocrine/genetic diseases, ovariectomy, malignancy therapy, etc.) until they reach normal menopausal age. In this age group, a specific benefit-risk assessment should be performed, including consideration of the etiology of premature menopause (surgical versus other causes).
Diagnosis and initiation of therapy in patients with premature menopause should preferably be performed in an appropriate center experienced in the treatment of this clinical picture.
Progyluton does not have a contraceptive effect. Non-hormonal contraceptive methods must be used if applicable.
Each white Progyluton sugar-coated tablet contains 46,2mg lactose and each light brown sugar-coated tablet contains 45.7 mg of lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicine.
Each white Progyluton sugar coated tablet contains 34 mg of sucrose and each light brown sugar-coated tablet contains 33,4 mg of sucrose. Patients with rare hereditary problems of fructose/galactose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not use this medicine.

Interactions

In order to identify potential interactions, the Information for Healthcare Professionals for the concomitant medicinal products should also be consulted.

Pharmacokinetic interactions

Effect of other medicinal products on the pharmacokinetics of Progyluton

Enzyme inducers

An increased clearance of sex hormones due to induction of hepatic enzymes can result in reduced plasma concentrations of oestrogens and/or progestogens, thereby reducing clinical efficacy and potentially causing irregular bleeding. This applies, for example, to barbiturates, bosentan, carbamazepine, felbamate, modafinil, oxcarbazepine, phenytoin, primidone, rifabutin, rifampicin and topiramate as well as to medicinal products containing St John’s wort (Hypericum perforatum).
Enzyme induction can be observed after just a few days and can last for at least 4 weeks or more after discontinuation of these medicinal products. Maximum enzyme induction is generally seen after a few weeks.

Enzyme inhibitors

Potent and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), macrolide antibiotics (e.g. clarithromycin, erythromycin), diltiazem, verapamil and grapefruit juice can increase the plasma concentrations of oestrogens and/or progestogens.

Active substances with varying effects on the clearance of sex hormones

Various HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease the plasma concentrations of oestrogens or progestogens if they are used concomitantly with an HRT. These changes may be clinically relevant in some cases.

Enterohepatic circulation

Pharmacokinetic interactions are not expected with concomitant short-term use (up to 10 days) of antibiotics that do not show any interactions with the CYP3A4 enzyme system. Insufficient data are available on possible interactions with long-term concomitant antibiotics use (e.g. in case of borreliosis or osteomyelitis). A reduction in drug levels due to an effect of the enterohepatic circulation cannot be ruled out.

Effect of Progyluton on the pharmacokinetics of other medicinal products

Sex hormones can also affect the pharmacokinetics of other medicinal products. Accordingly, their plasma concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine, see below).
An interaction study with lamotrigine, an anti-epileptic medicine, and a combined oral contraceptive (30 mcg ethinyl estradiol/150 mcg levonorgestrel) showed a clinically relevant increase in the clearance of lamotrigine with a correspondingly significant decrease in plasma lamotrigine levels when these drugs were administered concomitantly. Such a decrease in plasma concentrations may be associated with reduced seizure control. An adjustment of the lamotrigine dose may be necessary. Other hormonal contraceptives or HRT preparations were not investigated. However, it is expected that such preparations show a comparable potential for interaction. If a new treatment with Progyluton is started in patients taking lamotrigine, it may therefore be necessary to adjust the lamotrigine dose, and the lamotrigine concentrations should be closely monitored at the start of treatment.
If Progyluton is discontinued, lamotrigine levels may increase again, and the patient should also be monitored in this phase, with a possible reduction in the dose of lamotrigine.
Sex hormones can also affect the effect of oral anticoagulants.
Interactions with unknown mechanism
In clinical studies, when combined contraceptives containing ethinyl estradiol were administered concomitantly with specific combinations (ombitasvir / paritaprevir / ritonavir used in the treatment of HCV infections with or without dasabuvir; glecaprevir/pibrentasvir; sofosbuvir/velpatasvir/voxilaprevir) compared with patients who were exclusively treated with antivirals, there was a significantly more

frequent clinically relevant increase in ALT (including cases of an increase to more than five times the upper limit of normal). However, when using other oestrogens (in particular estradiol and estradiol valerate), the incidence of a transaminase increase was not higher than in patients without oestrogen therapy. Due to the limited number of women who took other such oestrogen-containing medicinal products, caution is generally required with concomitant administration of oestrogens with any of the above drugcombinations.

Pregnancy, lactation

Pregnancy

The use of Progyluton is contraindicated during pregnancy. If pregnancy occurs or is suspected during use, the medicinal product must be discontinued immediately.

Animal studies have shown evidence of foetal risks. However, most of the epidemiological studies conducted to date show no clear evidence of an embryotoxic or teratogenic effect when oestrogens or combinations of oestrogens and progestogens were accidentally administered during pregnancy.

Lactation

There is no indication for Progyluton during breast-feeding.

The medicinal product must not be used while breast-feeding, since milk production may be reduced, milk quality may be altered, and small concentrations of the substance may also be detected in breast milk.

Effects on ability to drive and use machines

No corresponding studies have been performed. Progyluton is not expected to have an effect on the ability to drive or use machines, however, compare with the section “Undesirable effects”.

Undesirable effects

The serious undesirable effects in connection with the use of HRT are also described in the “Warnings and precautions” section (see there).

The adverse reactions that were observed with HRT preparations are listed below by organ system and frequency. A connection with Progyluton cannot be confirmed or ruled out.

The frequency categories are defined as follows: (common ≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); (rare ≥ 1/10,000, < 1/1,000); not known (cannot be estimated from the available data).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Uncommon: breast cancer.

Not known: endometrial cancer.

Immune system disorders

Uncommon: hypersensitivity reactions.

Metabolism and nutrition disorders

Common: weight gain.

Not known: weight loss.

Psychiatric disorders

Common: mood swings, depression.
Uncommon: changes in libido*, nervousness.
Rare: anxiety.
* There have been reports of both decreased and increased libido.

Nervous system disorders

Common: headache.
Uncommon: sleep disorders, dizziness, migraine.

Eye disorders

Uncommon: Visual disturbances.

Cardiac disorders

Uncommon: palpitations, increase in blood pressure, arterial thromboembolic events (e.g. myocardial infarction, apoplexy)

Vascular disorders

Uncommon: venous thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism).

Gastrointestinal disorders

Common: flatulence, abdominal pain, nausea, dyspepsia.
Uncommon: vomiting.

Hepatobiliary disorders

Uncommon: abnormal liver function tests.
Very rare: cholestatic jaundice.
Not known: cholelithiasis (and other gallbladder diseases).

Skin and subcutaneous tissue disorders

Common: rash, pruritus.
Uncommon: acne, hirsutism, alopecia, urticaria.
Not known: chloasma, erythema nodosum, erythema multiforme, vascular purpura.

Musculoskeletal and connective tissue disorders

Common: back pain.
Uncommon: muscle cramps.

Reproductive system and breast disorders

Very common: feeling of tightness in the chest, chest pain, abnormal bleeding (menorrhagia, metrorrhagia, spotting, etc.).
Common: abdominal pain, vaginal discharge, enlarged uterine fibroids, breast enlargement.
Rare: dysmenorrhoea, premenstrual syndrome.
Not known: endometrial hyperplasia.

General disorders

Common: peripheral oedema, asthenia.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Due to the low acute toxicity of the active substances estradiol valerate and norgestrel, no acute risk of intoxication is expected, even in the event of a single inadvertent intake of many times the therapeutic dose.

An acute overdose may be associated with headache, nausea, vomiting, a feeling of tightness in the chest and uterine bleeding.

In the event of a chronic overdose, an increase in the undesirable effects and an increase in the risks described under “Warnings and precautions” can be expected.

There is no specific antidote, and any treatment must be symptomatic.

Properties/Effects

ATC code

G03FB01

Mechanism of action

Progyluton is a two-phase preparation for hormone replacement following menopause and for cycle regulation in younger women.

Estradiol

Following oral intake of estradiol valerate, the active substance estradiol is rapidly released. Estradiol, which is predominantly produced by ovarian follicles in women from menarche to menopause, is the most effective oestrogen on a receptor level (e.g., in uterus, vagina, urethra, breasts, hypothalamus, pituitary gland, osteoblasts and liver).
The loss of ovarian oestrogen causes vasomotor and thermoregulatory instability (hot flushes), sleep disorders, depressive moods and increasing atrophy of the genitourinary system in many women.

These disorders can largely be alleviated through oestrogen replacement. However, Progyluton has a favourable effect on depressive moods only if they occur in connection with vasomotor symptoms. Oestrogen replacement at doses that cause an improvement in menopausal symptoms also exerts a strong stimulating effect on mitosis and proliferation of the endometrium. Oestrogen monotherapy increases the frequency of endometrial hyperplasia and the risk of endometrial cancer. In Progyluton, estradiol valerate is cyclically combined with norgestrel, which largely prevents this risk.

Norgestrel

Norgestrel is a progestogen that essentially mimics the biological activities of the endogenous progestogen progesterone: this acts on all tissues that also contain oestrogen receptors, induces protein synthesis and simultaneously reduces the number of oestrogen and progesterone receptors, thereby limiting excessive stimulation of the growth in the target tissues triggered by oestrogen.
In the uterus, which is one of the most important target organs of progestogens, their activity induces secretory transformation of the endometrium proliferated under the influence of oestrogen. If the concentration of progestogen decreases, the endometrium built up by the effect of oestrogen is rejected.
The additional administration of a progestogen on 10–14 (preferably 12) days of each cycle of continuous oestrogen therapy largely prevents hyperstimulation of the endometrium that would be caused by oestrogen monotherapy. This considerably reduces the frequency of hyperplasia that can lead to irregular bleeding and endometrial cancer.
Progyluton is particularly suitable for women in perimenopause: it alleviates the typical subjective symptoms and regulates the cycle.
At a dose of 2 mg, estradiol valerate has a very low central inhibitory effect. When taking Progyluton, this generally does not result in inhibition of ovulation, and endogenous hormone production is barely affected. This is why the preparation can also be used for developing the cycle and regulating the cycle in younger women under certain conditions (“Warnings and precautions”).

Pharmacodynamics

See “*Mecanism of action*”

Clinical efficacy

No data

Pharmacokinetics

Estradiol valerate

Absorption

After oral administration, estradiol valerate is rapidly and completely absorbed. Cleavage of the steroid ester to estradiol and valeric acid takes place in the intestinal wall and during first passage

through the liver. As a result of first-pass metabolism, the bioavailability of estradiol is only approximately 3%.

Peak estradiol plasma concentrations (approx. 30 pg/mL) are generally reached 4–9 hours after taking a tablet.

The oestrogen levels between the treatment phase with estradiol valerate alone and that in combination with norgestrel show no relevant differences.

Concomitant intake of food has no influence on the bioavailability of estradiol compared to intake on an empty stomach.

Steady-state conditions

Around twice as high serum estradiol levels were observed with repeat administration in comparison to single doses. C_{min} is 30 pg/mL and C_{max} is 60 pg/mL on average in steady-state conditions.

Distribution

Around 60% of the estradiol is bound to albumin and almost 40% is bound to SHBG in plasma. Only 1–1.5% of estradiol is available as free substance in plasma.

The apparent volume of distribution of estradiol following single intravenous administration is approximately 1 L/kg.

Estradiol crosses the placenta.

Estradiol and its metabolites are excreted only in small quantities in breast milk.

Metabolism

After the ester cleavage of estradiol valerate, with the involvement of CYP3A4, there is a pronounced metabolism of estradiol in particular to estrone, estriol and estrone sulphate, which follows the biotransformation pathways of endogenous estradiol. The active main metabolite estrone reaches about 8 fold and estrone sulphate reaches about 150 fold the plasma concentrations of estradiol. The metabolic clearance of estradiol is approximately 10–30 mL/min/kg.

Elimination

The estradiol metabolites are conjugated at about 90% with glucuronide or sulfate and are excreted via the urine with a half-life of approximately one day. Only about 10% of the metabolites are eliminated via the faeces and undergo enterohepatic circulation.

Once treatment has ended, estradiol levels corresponding to those before treatment are reached within 2–3 days.

Norgestrel

Absorption

Norgestrel is rapidly and completely absorbed following oral administration. The active component of the racemate norgestrel is levonorgestrel, which is completely bioavailable. The peak plasma

concentration of levonorgestrel is generally 7–8 ng/mL and is reached 1–1.5 hours after a single dose of Progyluton.

Steady-state conditions

Following repeat administration, elevated trough levels of approximately 1 ng/mL were measured. However, there is no relevant difference in exposure (AUC) between the steady state and a single dose when administering the oestrogen and progestogen combination.

Distribution

Only about 1.3% of the total concentration of levonorgestrel in the serum is present as free steroid, around 64% is bound specifically to SHBG and around 35% non-specifically to albumin. The relative proportions of unbound, albumin-bound and SHBG-bound levonorgestrel depend heavily on SHBG concentration in plasma. At the end of the oestrogen-only phase of the Progyluton treatment cycle, the concentration of SHBG reaches its maximum and then drops to the minimum levels by the end of the combination phase. The estradiol-induced increase in SHBG concentration causes an increase in the SHBG-bound proportion and a decrease in the unbound fraction.
Approximately 0.1% of the administered dose is excreted in breast milk.

Metabolism

Levonorgestrel is extensively metabolized in the liver. The major metabolic degradation pathways are reduction of the Δ4-3-oxo group and hydroxylations at the 2α, 1β, and 16β positions, followed by conjugation. CYP3A4 is involved as the main enzyme in the oxidative metabolism of levonorgestrel. However, available in vitro data suggest that CYP-mediated biotransformation reactions may be of secondary importance in the metabolism of levonorgestrel compared with reduction and conjugation. Pharmacologically active metabolites of levonorgestrel are unknown.

Elimination

Levonorgestrel undergoes biphasic elimination. Clearance is approximately 1 mL/min/kg.
The metabolites are excreted with a half-life of about 1 day at roughly equal proportions via the urine and bile.

Kinetics in specific patient groups

Hepatic impairment

The pharmacokinetics of Progyluton has not been investigated in patients with hepatic impairment. However, the metabolic degradation of oestrogens and progestogens is known to be slowed in case of hepatic impairment (see also “Warnings and precautions”).

Renal impairment

The pharmacokinetics of Progyluton has not been investigated in patients with renal impairment.

Children and adolescents

No data are available on the pharmacokinetics of estradiol valerate or norgestrel in adolescents after menarche.

Preclinical data

Carcinogenicity

Pre-clinical studies with estradiol and combinations of estradiol and progestogens on repeated dose toxicity, genotoxicity and carcinogenicity reveal no clear evidence of special hazards for humans, even though epidemiological studies and animal studies with estradiol were able to show an increased risk of carcinogenicity.

Embryotoxicity/teratogenicity

Reproductive toxicity studies with levonorgestrel do not indicate a teratogenic potential or a risk of virilisation of female foetuses, which is associated with the partially androgenic effect of levonorgestrel at therapeutic doses. However, pregnancy is a contraindication for the use of Progyluton.
The serum concentrations of estradiol achieved when using estradiol valerate are in the physiological range.

Mutagenicity

In vitro and *in vivo* studies with 17-beta-estradiol or with levonorgestrel (i.e., the pharmacologically active enantiomer of norgestrel) yielded no evidence of a mutagenic potential.

Other information

Effects on diagnostic methods

Sex hormones may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of binding proteins and lipid/lipoprotein fractions, parameters of carbohydrate metabolism as well as parameters of coagulation and fibrinolysis. The changes generally remain within the reference range.

Shelf life

60 months
Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Keep out of reach of children.
Do not store above 30°C.

Authorisation number

37987 (Swissmedic).

Packs

Calendar pack of 1 × 21 and 3 × 21 sugar-coated tablets (B)

Marketing authorisation holder

Bayer (Schweiz) AG, Zurich, Switzerland.

Date of revision of the text

January 2022.