MENARINI

Progyluton®

Coated Tablets

1. NAME OF THE MEDICINAL PRODUCT

Progyluton Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each white coated tablet contains estradiol valerate 2.0 mg

Each light brown coated tablet contains estradiol valerate 2.0 mg and norgestrel 0.5 mg

For a full list of excipient(s) see section "list of excipients"

3. PHARMACEUTICAL FORM

Coated tablet

4. CLINICAL PARTICULARS

4.1 Indication(s)

Hormone replacement therapy (HRT) for the treatment of signs and symptoms of estrogen deficiency due to menopause or hypogonadism, castration or primary ovarian failure in women with an intact uterus.

Prevention of postmenopausal osteoporosis.

Control of irregular menstrual cycles.

Treatment of primary or secondary amenorrhea.

4.2 Dosage and method of administration

4.2.1 Method of administration

Oral Use

4.2.2 Dosage regimen

- How to start Progyluton

If the patient is still menstruating, treatment should begin on the 5th day of the cycle (1st day of menstrual bleeding = 1st day of the cycle).

Patients with amenorrhea or very infrequent periods or who are postmenopausal may start at any time, provided pregnancy has been excluded (see section 'Pregnancy and lactation').

- Dosage

One white tablet is taken daily for the first 11 days, followed by one light brown tablet daily for 10 days.

Following the 21 days of tablet-taking there will be a tablet-free interval of 7 days.

- Administration

Each pack covers 21 days of treatment. A new pack of Progyluton should be started after the 7-day tablet-free interval on the same day of the week as the previous one.

The tablets are to be swallowed whole with some liquid.

The tablets should preferably be taken at the same time every day.

- Missed tablets

In case a tablet is forgotten, it should be taken as soon as possible. If more than 24 hours have elapsed, no extra tablet needs to be taken. If several tablets are forgotten, bleeding may occur.

Bleeding usually occurs during the tablet-free interval of 7 days within a few days after the last tablet was taken.

4.2.3 Additional information on special populations

4.2.3.1 Pediatric patients

Progyluton is not indicated for use in children and adolescents.

4.2.3.2 Geriatric patients

There are no data suggesting a need for dosage adjustment in elderly patients.

4.2.3.3 Patients with hepatic impairment

Progyluton has not been specifically studied in patients with hepatic impairment. Progyluton is contraindicated in women with presence or history of liver tumors and with severe hepatic disease (see section 'Contraindications'). For women with impaired liver function, close supervision is needed and in case of deterioration of markers of liver function, use of HRT should be stopped (see section 'Special warnings and precautions for use').

4.2.3.4 Patients with renal impairment

Progyluton has not been specifically studied in renally impaired patients.

4.3 Contraindications

Hormone replacement therapy (HRT) should not be started in the presence of any of the conditions listed below. Should any of the conditions appear during HRT use, the product should be stopped immediately.

- Pregnancy and lactation
- Undiagnosed vaginal bleeding
- Known or suspected cancer of the breast
- Known or suspected premalignant conditions or malignancies, if sex steroid-influenced
- Presence or history of liver tumors (benign or malignant)
- Severe hepatic disease
- Acute arterial thromboembolism (e.g. myocardial infarction, stroke)
- Active deep venous thrombosis, thromboembolic disorders, or a documented history of these conditions
- A high risk of venous or arterial thrombosis
- Severe hypertriglyceridemia
- Known hypersensitivity to any of the components of Progyluton

4.4 Special warnings and special precautions for use

Before initiating therapy, all conditions/risk factors mentioned below should be considered when determining the individual benefit/risk of treatment for the patient.

During HRT use, **therapy should be discontinued immediately** in case a contraindication is discovered, as well as in the following situations:

- Migrainous or frequent and unusually severe headaches that occur for the first time or other symptoms that are possible prodroma of cerebrovascular occlusion.
- Recurrence of cholestatic jaundice or cholestatic pruritus which occurred first during pregnancy or previous use of sex steroids.
- Symptoms of a thrombotic event or suspicion thereof.

In the event of new onset or deterioration of the following conditions or risk factors, the individual benefit/risk analysis should be re-done, taking into consideration the possible necessity of discontinuing therapy.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. HRT should not be prescribed in case of a negative risk benefit assessment.

- Venous thromboembolism

Both randomized-controlled and epidemiological studies have suggested an increased relative risk (RR) of developing venous thromboembolism (VTE), i.e. deep venous thrombosis or pulmonary embolism. Benefit/Risk should therefore be carefully weighed in consultation with the patient when prescribing HRT to women with a risk factor for VTE.

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic disposition) and severe obesity. The risk of VTE also increases with age. There is no consensus about the possible role of varicose veins in VTE.

The risk of VTE may be temporarily increased with prolonged immobilization, major elective or posttraumatic surgery, or major trauma. Depending on the nature of the event and the duration of the immobilization, consideration should be given to a temporary discontinuation of HRT.

- Arterial thromboembolism

Two large clinical trials with continuous combined conjugated estrogens (CEE) and medroxyprogesterone acetate (MPA) showed a possible increased risk of coronary heart disease (CHD) in the first year of use and no benefit thereafter. One large clinical trial with CEE alone showed a potential reduction of CHD rates in women aged 50-59 and no overall benefit in the total study population. As a secondary outcome, in two large clinical trials with CEE alone or combined with MPA a 30-40% increased risk of stroke was found. It is uncertain whether these findings also extends to other HRT products or non-oral routes of administration.

- Gallbladder disease

Estrogens are known to increase the lithogenicity of the bile. Some women are predisposed to gallbladder disease during estrogen therapy.

- Dementia

There is limited evidence from clinical studies with CEE-containing preparations that hormonal treatment may increase the risk of probable dementia if initiated in women aged 65 or older. The risk may be decreased if treatment is initiated in the early menopause, as observed in other studies. It is unknown whether these findings also extend to other HRT products.

Tumors

- Breast cancer

Clinical and observational studies have reported an increased risk of having breast cancer diagnosed in women taking HRT for several years.

Estimates for the overall relative risks of breast cancer diagnosis given in more than 50 epidemiological studies ranged in the majority of the studies between 1 and 2.

The relative risk increases with duration of treatment and may be lower or possibly neutral with estrogenonly products.

Two large randomized trials with CEE alone or continuously combined with MPA showed risk estimates of 0.77 (95%CI: 0.59-1.01) or 1.24 (95% confidence interval (CI): 1.01-1.54) after 6 years of HRT use. It is unknown whether the increased risk also extends to other HRT products.

The excess risk decreases within a few years after stopping HRT.

HRT increases the density of mammographic images which may adversely affect the radiological detection of breast cancer in some cases.

- Ovarian cancer

A meta-analysis from 52 epidemiological studies reported that the overall risk of being diagnosed with ovarian cancer is slightly increased for users of HRT compared to women who have never used HRT (prospective studies: RR 1.20, 95% CI 1.15-1.26; all studies combined: RR 1.14, 95% CI 1.10-1.19). In women currently using HRT the risk of ovarian cancer was further increased (RR 1.43, 95% CI 1.31-1.56).

These associations have not been shown in all studies including randomised controlled trials, e.g. the Women's Health Initiative (WHI).

Furthermore, an effect of duration of exposure has not been consistently shown, but the risk may be more relevant with long-term use (several years).

- Endometrial cancer

Prolonged exposure to unopposed estrogens increases the risk of development of endometrial hyperplasia or carcinoma.

- Liver tumor

In rare cases benign, and even more rarely, malignant liver tumors have been observed after the use of hormonal substances such as those contained in HRT products. In isolated cases, these tumors led to lifethreatening intra-abdominal hemorrhage.

Other conditions

A general association between HRT use and development of clinical hypertension has not been established. Small increases in blood pressure have been reported in women taking HRT. Clinically relevant increases are rare. However, if in individual cases a sustained clinically significant hypertension develops during the use of HRT then withdrawing the HRT may be considered.

Non-severe disturbances of liver function, including hyperbilirubinemias such as Dubin-Johnson syndrome or Rotor syndrome, need close supervision and liver function should be checked periodically. In case of deterioration of markers of liver function use of HRT should be stopped.

Women with moderately elevated levels of triglycerides need special surveillance. HRT in these women may be associated with a further increase of triglyceride levels bearing the risk of acute pancreatitis.

Although HRT may have an effect on peripheral insulin resistance and glucose tolerance, there is generally no need to alter the therapeutic regimen in diabetics using HRT. However, diabetic women should be carefully monitored while taking HRT.

Certain patients may develop undesirable manifestations of estrogenic stimulation under HRT such as abnormal uterine bleeding. Frequent or persistent abnormal uterine bleeding during treatment is an indication for endometrial assessment.

If the treatment of irregular menstrual cycles is not successful, organic diseases must be ruled out by means of adequate diagnostic measures.

Uterine fibroids (myomas) may increase in size under the influence of estrogens. If this is observed, treatment should be discontinued.

Should endometriosis be reactivated under treatment, discontinuation of therapy is recommended.

Close medical supervision (including periodic measurement of prolactin levels) is necessary if the patient suffers from prolactinoma.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking HRT.

The following conditions have been reported to occur or deteriorate with HRT use. Although the evidence of an association with HRT use is inconclusive, women with these conditions and treated with HRT should be carefully monitored.

Epilepsy
Benign breast disease
Asthma
Migraine
Porphyria
Otosclerosis
Systemic lupus erythematosus
Chorea minor

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

4.5 Interaction with other medicinal products and other forms of interaction

- ***Effects of other medicinal products on Progyluton***

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to changes in the uterine bleeding profile and/or reduction of the therapeutic effect.

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme-induction), e.g.:

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John´s wort.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Substances with variable effects on the clearance of sex hormones

When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the estrogen or progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of sex hormones (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestin or both.

Substances which undergo substantial conjugation (e.g. paracetamol) may increase the bioavailability of estradiol by competitive inhibition of the conjugation system during absorption.

- **Interaction with alcohol**

Acute alcohol ingestion during use of HRT may lead to elevations in circulating estradiol levels.

Other forms of interaction

- Laboratory tests

The use of sex steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism, and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range

4.6 Pregnancy and lactation

HRT is not indicated for use during pregnancy or lactation.

4.6.1 Pregnancy

If pregnancy occurs during medication with Progyluton, treatment should be discontinued immediately.

4.6.2 Lactation

Small amounts of sex hormones may be excreted in human milk.

4.7 Effects on ability to drive or use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of Progyluton

4.8 Undesirable effects

4.8.1 Summary of the safety profile

The most serious undesirable effects associated with the use of hormone replacement therapy are listed in section 'Special warnings and precautions for use'.

4.8.2 Tabulated list of adverse reactions

Other undesirable effects that have been reported in users of hormone replacement therapy (post-marketing data) but for which the association to Progyluton has neither been confirmed nor refuted are:

System Organ Class MedDRA v. 8.0	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
Immune system disorders		Hypersensitivity reaction	
Metabolism and nutrition disorders	Weight increase Weight decrease		
Psychiatric disorders		Depressed mood	Anxiety, Libido decreased Libido increased
Nervous system disorders	Headache	Dizziness	Migraine
Eye disorders		Visual disturbances	Contact lens intolerance
Cardiac disorders		Palpitations	
Gastrointestinal disorders	Abdominal pain, Nausea	Dyspepsia	Bloating, Vomiting
Skin and subcutaneous tissue disorders	Rash, Pruritus	Erythema nodosum, Urticaria	Hirsutism, Acne
Musculoskeletal and connective tissue disorders			Muscle cramps
Reproductive system and breast disorders	Uterine/Vaginal bleeding including Spotting (bleeding irregularities usually subside during continued treatment)	Breast pain, Breast tenderness	Dysmenorrhea, Vaginal discharge, Premenstrual-like syndrome, Breast enlargement
General disorders and administration site conditions		Edema	Fatigue

The most appropriate MedDRA term (version 8.0) to describe a certain reaction is listed.

4.8.3 Description of selected adverse reactions

Synonyms or related conditions are not listed, but should be taken into account as well.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema (see section 'Special Warnings and special precautions for use').

Estrogen-only and combined estrogen-progestin HRT has been associated with a slightly increased risk of ovarian cancer in epidemiological studies. The risk may be more relevant with long-term use (several years) (see section 'Special warnings and precautions for use').

4.9 Overdose

Acute toxicity studies did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. Overdosage may cause nausea and vomiting and withdrawal bleeding may occur in some women. There is no specific antidote and treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.1.1 Mechanism of action

The estrogen in Progyluton is estradiol valerate, a prodrug of the natural human 17ß-estradiol. The constituent norgestrel is a synthetic progestogen. With the composition and the sequential regimen of Progyluton, including an estrogen monophase for 11 days, an estrogen-progestogen combination for 10 days and a treatment-free interval of 7 days, a menstrual cycle is established in women with an intact uterus, provided the preparation is taken regularly.

Ovulation is not inhibited during the use of Progyluton, and the endogenous production of hormones is hardly affected. The preparation can be employed in younger women to develop and regulate the cycle as well as in perimenopausal women to treat irregular uterine bleeding.

5.1.2 Pharmacodynamic effects

During the climacteric, the reduction and finally loss of ovarian estradiol secretion can result in instability of thermoregulation, causing hot flushes associated with sleep disturbance and excessive sweating, and urogenital atrophy with symptoms of vaginal dryness, dyspareunia and urinary incontinence. Less specific but often mentioned as part of the climacteric syndrome are symptoms like anginal complaints, palpitations, irritability, nervousness, lack of energy and concentration abilities, forgetfulness, loss of libido and joint and muscle pain.

5.1.3 Clinical efficacy and safety

Hormone replacement therapy (HRT) alleviates many of these symptoms of estradiol deficiency in the menopausal woman.

HRT with an adequate estrogen dosage like in Progyluton reduces bone resorption and retards or halts postmenopausal bone loss. Long-term treatment with HRT has been shown to reduce the risk of peripheral fractures in postmenopausal women. When HRT is discontinued, bone mass declines at a rate comparable to that in the immediate postmenopausal period. There is no evidence that HRT restores bone mass to premenopausal levels. HRT also has a positive effect on skin collagen content and skin thickness and can retard the process of skin wrinkling.

HRT changes the lipid profile. It lowers total cholesterol and LDL-cholesterol and may increase HDL-cholesterol and triglyceride levels. The metabolic effects may be counteracted to some extent by the addition of a progestogen like in Progyluton.

The addition of a progestogen to an estrogen replacement regimen for at least 10 days per cycle as in Progyluton reduces the risk of endometrial hyperplasia and the attendant risk of adenocarcinoma in women with an intact uterus. The addition of a progestogen to an estrogen replacement regimen has not been shown to interfere with the efficacy of estrogen for its approved indications.

Observational studies and the Women's Health Inititative (WHI) trial on conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) suggest a reduction of colon cancer morbidity in postmenopausal women taking HRT. In the WHI trial on CEE mono-therapy a risk reduction was not observed. It is unknown whether these findings also extend to other HRT products.

5.2 Pharmacokinetic properties

5.2.1 Estradiol valerate

5.2.1.1 Absorption

Estradiol valerate is rapidly and completely absorbed. The steroid ester is cleaved into estradiol and valeric acid during absorption and the first liver passage. At the same time, estradiol undergoes extensive further metabolism, e.g. into estrone, estriol and estrone sulfate. Only about 3 % of estradiol becomes bioavailable after oral administration of estradiol valerate. Food does not affect the bioavailability of estradiol.

5.2.1.2 Distribution

Maximum concentrations of estradiol in serum of approx. 30 pg/ml are generally reached between 4-9 hours after tablet intake. Within 24 hours after tablet intake, serum levels of estradiol declined to concentrations of about 15 pg/ml. Estradiol binds to albumin and the sex hormone binding globulin (SHBG). However, the binding to SHBG is lower than that of levonorgestrel. The unbound fraction of estradiol in serum is about 1-1.5 % and the SHBG-bound fraction is in the range of 30-40 %.

The apparent volume of distribution of estradiol after single intravenous administration is about 1 l/kg.

5.2.1.3 Metabolism

After the ester cleavage of the exogenously administered estradiol valerate, the metabolism of the drug follows the biotransformation pathways of endogenous estradiol. Estradiol is mainly metabolized in the liver but also extrahepatically e.g. in gut, kidney, skeletal muscles and target organs. These processes involve the formation of estrone, estriol, catecholestrogens and sulfate and glucuronide conjugates of these compounds, which are all distinctly less estrogenic or even nonestrogenic.

5.2.1.4 Elimination

The total serum clearance of estradiol following single intravenous administration, shows high variability in the range of 10- 30 ml/min/kg. A certain proportion of estradiol metabolites are excreted in the bile and undergo a so-called enterohepatic circulation. Ultimately estradiol metabolites are mainly excreted as sulfates and glucuronides with the urine.

5.2.1.5 Steady state conditions

In relation to the single dose, approximately two times higher serum levels of estradiol are observed after multiple administration. On average, the concentration of estradiol varies between 30 (minimum levels) and 60 pg/ml (maximum levels). Estrone, as a less estrogenic metabolite, reaches about 8 times higher concentrations in serum, estrone sulfate reaches approximately 150-times higher concentrations. After stopping the treatment with Progyluton, pre-treatment levels of estradiol and estrone are reached within 2-3 days. No distinct difference in the estrogen levels is observed between the treatment phase with estradiol valerate alone or in combination with norgestrel.

5.2.2 Norgestrel

5.2.2.1 Absorption

After oral administration, norgestrel is rapidly and completely absorbed. The active component of the racemate norgestrel is levonorgestrel which becomes completely bioavailable from the racemate and accounts for about half of the dose of norgestrel.

5.2.2.2 Distribution

On an average, maximum concentrations of levonorgestrel in serum of 7-8 ng/ml are already reached within 1-1.5 hours after a single administration of Progyluton. Subsequently, serum levels of levonorgestrel decline biphasically with a mean terminal half-life of 27 hours and reach minimum concentrations of about 1 ng/ml 24 hours post dose.

Levonorgestrel binds to albumin and SHBG. Only about 1-1.5 % of the total levonorgestrel concentration in serum is not protein-bound. The relative fractions of free, albumin- and SHBG-bound levonorgestrel are strongly dependent on the concentration of SHBG in serum. After induction of the binding proteins, the fraction bound to SHBG increases whereas the unbound fraction and that bound to albumin decreases. At the end of the estrogen monophase of the Progyluton treatment cycle, the concentration of SHBG reaches the highest levels in serum which then decreases to the lowest levels at the end of the combination phase. Accordingly, the free fraction of levonorgestrel amounts to about 1 % at the beginning and about 1.5 % at the end of the combination phase. The corresponding fractions of levonorgestrel bound to SHBG are 70 and 65 %, respectively.

5.2.2.3 Metabolism

Norgestrel is extensively metabolized. The most important metabolic pathways of the active substance levonorgestrel (LNG) are the reduction of the Δ4-3-oxo group and hydroxylations at position 2α, 1β and 16β, followed by conjugation. CYP3A4 is the main enzyme involved in the oxidative metabolism of LNG. The available in vitro data suggest that CYP mediated biotransformation reactions may be of minor relevance for LNG compared to reduction and conjugation. Pharmacologically active metabolites are not known.

5.2.2.4 Elimination

The total clearance rate of levonorgestrel from serum is 1 ml/min/kg.

With a half-life of about 1 day, approximately the same proportions of the metabolites of norgestrel are excreted with the urine and the bile.

5.2.2.5 Steady-state conditions

Based on the elimination half-life of levonorgestrel in serum of about 24 hours, an accumulation of the active substance in serum would be expected. Accordingly, elevated trough levels of about 1 ng/ml are observable after repeated administration. However, due to the simultaneous change in the protein binding capacity during treatment (decrease in SHBG concentration), the area under the serum levels-time course of levonorgestrel does not really differ between the beginning and the end of the 10 day treatment phase with the estrogen/progestogen combination. Thus, no accumulation of levonorgestrel in serum is observed after multiple administration of Progyluton.

5.3 Preclinical safety data

5.3.1 Carcinogenicity

The results from toxicity studies with repeated administration including tumorigenicity studies with the two active substances are not suggestive of a particular risk related to use in humans. However, it has to be born in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumors.

5.3.2 Embryotoxicity/teratogenicity

Reproductive toxicity studies with levonorgestrel (LNG) did not indicate a teratogenic potential nor a risk of a virilization of female fetuses related to the androgenic partial effect of LNG at therapeutic dose levels. However, pregnancy is a contraindication for the use of Progyluton.

As no non-physiological estradiol-serum-concentrations are produced by administration of estradiol valerate, there is no evidence of a risk to the fetus due to this component of the preparation.

5.3.3 Mutagenicity

In vitro and in vivo studies with 17ß-estradiol or with LNG (i.e. the pharmacologically active enantiomer of norgestrel) gave no indications of a mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

List of excipients

calcium carbonate
ferric oxide pigment, red
ferric oxide pigment, yellow
glycerol 85%
glycol montanate
lactose monohydrate
macrogol 6000 magnesium stearate
maize starch
povidone 25
providone 90
sucrose
talc
titanium dioxide

Nature and contents of container

Progyluton tablets are contained in blister packs consisting of transparent films made of polyvinyl chloride and metallic foils made of aluminum (mat side hot sealable).

Blister pack containing 21 tablets

Special precautions for storage

Store below 30°C

Store all drugs properly and keep them out of reach of children.

Manufacturer

Bayer Weimar GmbH und Co. KG
Dobereinerstrasse 20
99427 Weimar
Germany

Date of Revision of Text

January 2026