1. **NAME OF THE MEDICINAL PRODUCT**

Progyluton

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Active substances:
Calendar-pack containing 11 white tablets of 2 mg estradiol valerate each, plus 10 light brown tablets of 2 mg estradiol valerate and 0.5 mg norgestrel each.

Excipients:
Each white coated tablet contains 46.220 mg lactose monohydrate.
Each light brown coated tablets contain 45.720mg lactose monohydrate

3. **PHARMACEUTICAL FORM**

Coated tablets.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic Indications

Two phase preparation for climacteric and cycle disturbances.

4.2 Posology and method of administration

Progyluton is a cyclic HRT product. One tablet is to be taken orally once a day for 21 days, followed by a 7-day tablet free interval. Therefore each new pack is started after a 28 day cycle. The white tablets should be taken from days 1 to 11 followed by the brown tablets from days 12 to 21. It is recommended that the tablets are taken at the same time every day.

For initiation and continuation of treatment of peri- and post-menopausal symptoms the lowest effective dose for the shortest duration (see also *'Special warnings and special precautions for use'*) should be used.

For women still having periods, the first tablet should be taken on the 5th day of their menstrual period. If menstruation has stopped, or is infrequent or sporadic, then the first tablet can be taken any time.

If the patient is being transferred from a continuous HRT product, the patient may start Progyluton on any convenient day. For those transferring from a cyclic or sequential product, Progyluton should be started following completion of the previous regimen.

If a tablet is missed, it should be taken as soon as possible, unless it is more than 12 hours late. In this case the missed tablet should be left in the pack and the next tablet taken at the right time. Missing a dose may result in breakthrough bleeding or spotting.

Unless there is a previous diagnosis of endometriosis, it is not recommended that progestogen-containing HRT be given to hysterectomised women.

Children and adolescents
There are no data available on the safety and efficacy in children and adolescents under 18 years of age. Progyluton is not indicated for use in children and adolescents

Geriatric patients
There are no data suggesting a need for dosage adjustment in women aged 65 years or older (see section 4.4 Special warnings and precautions for use)

Patients with renal impairment
Progyluton has not been specifically studied in renally impaired patients. Available data do not suggest a need for dosage adjustment in this patient population

Hepatic insufficiency

Progyluton has not been tested in patients with hepatic insufficiency. Progyluton is contraindicated in women with serious hepatic conditions.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients,
- present or suspected breast cancer,
- a present or suspected sex-hormone dependent premalignant or malignant disease,
- untreated endometrial hyperplasia,
- unclarified vaginal bleeding,
- present or past benign or malignant hepatic tumors,
- serious liver conditions (including in the medical history), if the liver function values have not returned to normal,
- present or past venous thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism),
- acute or recent arterial thrombotic events (cerebral or myocardial infarction),
- presence of risk factors for arterial or venous thromboembolic events (e.g. antithrombin, protein S or protein C deficiency),
- severe hypertriglyceridemia,
- porphyria,
- pregnancy and lactation.

4.4 Special warnings and precautions for use

Every hormone replacement therapy (HRT) must be preceded by a clinical check on general health and a thorough gynecological examination, and the latter should be repeated at least once a year. The patient’s own and her family’s medical history should also be taken into account. The risk-benefit ratio must be carefully weighed up for each patient prior to the start

of therapy and should be reviewed regularly during treatment. The lowest possible dosage and the shortest possible duration of treatment should always be selected.

Before starting treatment, pregnancy should be excluded. If withdrawal bleeding fails to occur at about 28-day intervals, the possibility of pregnancy should be considered in peri-menopausal women.

Reasons for immediate discontinuation of therapy

If any of the above contraindications should occur during HRT therapy or in any of the following situations, treatment must be discontinued immediately:

- symptoms of a venous or arterial thromboembolic event or suspicion of the same; these also include:
    - first onset of migraine-like headaches or more frequent occurrence of unusually severe headaches
    - sudden partial or total loss of vision
    - sudden hearing disorders
- clinically relevant blood pressure increase,
- deterioration of liver function or occurrence of jaundice or hepatitis,
- perceptible growth of myomas,
- increase in epileptic seizures,
- pregnancy.

Circumstances that require special monitoring

If the following complaints exist, have recently occurred and/or have deteriorated during a pregnancy or during a previous hormone treatment, the patient should be monitored carefully. It should be taken into consideration that these complaints may recur or worsen during treatment with Progyluton:

- risk factors for estrogen-dependent tumors (e.g. stage 1 mammary carcinoma in relatives),
- benign breast changes,
- endometrial hyperplasia (including in the medical history),
- leiomyoma or endometriosis,
- risk factors for thromboembolic diseases (see also section entitled "Thromboembolic diseases"),
- migraine,
- hypertension,
- diabetes mellitus,
- hypertriglyceridemia,
- diseases of the liver or gallbladder,
- asthma,

- epilepsy,
- systemic lupus erythematosus,
- chorea minor,
- otosclerosis.

If any of the following conditions or risk factors apply for the first time or are exacerbated, the individual risk/benefit analysis must be reviewed, terminating therapy if necessary.

Tumors

Breast cancer

Randomized controlled studies and epidemiological investigations showed an enhanced risk of developing breast cancer among women who were given 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. Prior to the start of HRT all women must therefore undergo breast examination by a doctor once a year, and self-examinations of the breast should be performed once a month. Depending on age and the respective risk factors, a mammogram may also be indicated. The users should be informed of which breast changes they must report to their doctor.

A two large analysis of epidemiological studies revealed that the risk of contracting breast cancer increases with the duration of HRT and decreases after discontinuation of HRT. The time to return to age-appropriate risk baseline depends on the duration of previous HRT. 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, randomized study of more than 8,000 elderly, postmenopausal women (age at the start of the study 50-79, mean age 63), showed that, in comparison to placebo under combined HRT with conjugated estrogens and medroxyprogesterone acetate (MPA) after an average administration period of 5.6 years, there was an increase in invasive breast cancer in the estrogen/progestogen group (RR 1.24 [95% CI 1.02-1.50]).. For the estrogen monotherapy, on the other hand, there was no enhanced risk (RR 0.77 [95% CI 0.59-1.01]).

The Million Women Study, a nonrandomized cohort study, recruited 1,084,110 women. The average age of the women on entering the study was 55.9 years. Half of the women received HRT before and/or at the beginning of the study, the other half had never been given HRT. 9,364 cases of invasive breast cancer and 637 deaths due to breast cancer were recorded after an average observation period of 2.6 and 4.1 years, respectively. Women who were using HRT at the beginning of the study demonstrated, in comparison with the women who had never received such a therapy, a higher morbidity risk (RR 1.66 [95% CI 1.58-1.75]) and possibly, but less pronounced, a higher mortality from breast cancer (RR 1.22 [95% CI 1.00-1.48]). The highest risk was seen in the combined estrogen/progestogen therapy group (RR 2.00 [95% CI 1.88-2.12]). The relative risk was 1.30 (95% CI 1.21-1.40) for the estrogen monotherapy. The results were similar for the different estrogens and progestogens, for the various doses and administration routes and for continuous and sequential therapy. With all the types of HRT the risk increased with the duration of administration.

HRT increases opacity in mammographic images, and this can impair the radiological detection of breast cancer in some cases.

Endometrial carcinoma

Prolonged administration of estrogen increases the risk of developing endometrial hyperplasia or endometrial carcinoma. Studies suggest that this increased risk is largely minimized by the additional administration of a progestogen.

Medical monitoring is necessary for all women who use an HRT. All cases of abnormal bleeding (irregular, heavy or persistent bleeding, including spotting) must be investigated by means of appropriate diagnostic techniques (if applicable, including a histological investigation of the endometrium) in order to rule out an organic cause or a malignant finding.

Ovarian carcinoma

Several epidemiological studies suggest that HRT may be associated with an enhanced risk of developing epithelial ovarian carcinoma. An increased risk was found both for estrogen monotherapy and for combined HRT. While most studies revealed an increased risk only after long-term use (i.e.at least 5 years), no such relationship with the duration of administration was found in a meta-analysis published in 2015 (taking into consideration a total of 17 prospective and 35 retrospective studies).

In the prospective, randomized, placebo controlled WHI study, a statistically nonsignificant increased risk was found (HR 1.41; 95% CI 0.75-2.66).

Since ovarian carcinoma occurs much more rarely than breast cancer, the absolute increased risk is low in women who are using or have recently used an HRT.

Hepatic tumors

In rare cases after the use of hormonal active ingredients such as those that are contained in Progyluton, benign changes, and even more rarely malignant changes, in the liver have been observed, which in isolated cases led to life-threatening hemorrhages in the abdominal cavity. For this reason, a hepatic tumor should be included in differential diagnosis considerations, if severe upper abdominal pain, liver engorgement or signs of an intraabdominal hemorrhage occur.

Coronary heart disease and stroke

HRT should not be employed to prevent cardiovascular diseases.

Major clinical studies failed to show any positive effect in the primary prophylaxis (WHI study) or secondary prophylaxis (HERS study) of cardiovascular diseases.

The WHI study showed, in postmenopausal women who received an oral HRT with conjugated estrogens and MPA for an average of 5.2 years, an increased risk of cardiovascular events compared with placebo (RR 1.24 [95% CI 1.00-1.54], absolute increase in the risk = 6 cases per 10,000 women years). The risk was highest in the first year of HRT (RR 1.81 [95% CI 1.09-3.01]). The risk increased with the length of time since the menopause (menopause <10 years: RR 0.89; menopause 10-19 years: RR 1.22; menopause ≥20 years: RR 1.71).

Likewise, the cerebrovascular risk in the WHI study was seen to be enhanced in the combined estrogen/progestogen therapy cohort (RR 1.31 [95% CI 1.02-1.68]).

In the estrogen/monotherapy arm of the WHI study no significant effect on the cardiovascular risk was detected (RR 0.91 [95% CI 0.75-1.12]). On the other hand, the risk for cerebrovascular insults was enhanced (RR 1.39 [95% CI 1.10-1.77]).

The Heart and Estrogen/Progestin Replacement Study (HERS and HERS II), a prospective, placebo-controlled, randomized study, showed in more than 1,300 postmenopausal women with pre-existing coronary heart condition (mean age at inclusion in study 67 years), who received an oral HRT with conjugated estrogens and MPA for an average of 4.1 years (HERS) and 2.7 years (HERS II), no reduction in the cardiovascular risk. The relative risk was 0.99 (95% CI 0.84-1.17). The risk was highest in the first year of HRT (RR 1.52 [95% CI 1.01-2.29]).

Only limited data is available on HRT with the therapy starting at a relatively young age (for example, before the age of 55). This data suggests that the increase in the cardiovascular risk while undergoing HRT could be less in younger patients who have gone through menopause more recently than in the population (which tended to be older) investigated in the above-mentioned studies. However, this is not the case for cerebrovascular events.

The relative risk for cerebrovascular events is independent of age or the time since menopause. However, since the basic risk of a stroke depends strongly on age, the overall risk increases with advancing age for women undergoing HRT.

Alternative therapies should be considered for women already possessing risk factors for the development of cardiovascular or cerebrovascular events.

Venous thromboembolism (VTE)

HRT is associated with an enhanced risk for VTE, (e.g. deep vein thrombosis, pulmonary embolism).

Two controlled randomized studies (HERS and WHI) and several epidemiological studies revealed a 2-3-fold risk increase among women on HRT as compared with women who had never received such therapy. In particular, the WHI study demonstrated an enhanced incidence of pulmonary embolisms. The absolute rise in risk among women on HRT was 8 cases in 10,000 women years (15 as against 7), the relative risk being 2.13 (95% CI 1.39-3.25).

The heightened risk was only found in women currently on HRT and not among women who had had HRT in the past. The risk appears to be higher in the first few years of administration.

Even in the estrogen monotherapy arm of the WHI study, the risk of venous thromboembolism tended to increase. The relative risk of deep venous thrombosis was 1.47 (95% CI 0.87-2.47), and that of a pulmonary embolism was 1.34 (95% CI 0.70-2.55).

Among nonusers the number of VTE cases over a period of 5 years within the age group of 50-59 years was estimated to be 3 out of 1,000 women and in the age group of 60-69 years 8 out of 1,000 women. Among healthy women who take HRT for 5 years an additional 2-6 cases per 1,000 women occur among the age group 50-59 and 5-15 additional cases in the 60-69 year age bracket.

If corresponding symptoms or a suspected VTE occurs, the preparation must be discontinued immediately. Patients with risk factors for thromboembolic events should be closely monitored. In such women the risk-benefit ratio must be weighed up carefully and, if possible, other therapies should be considered.

The known risk factors for the occurrence of VTE include a corresponding medical history of the patient or her family's medical history (the occurrence of VTE in a close relative at a relatively young age may point to a genetic disposition), smoking, significant excess weight, systemic lupus erythematosus and malignant diseases.

Considering women with a combination of risk factors or a more highly pronounced single risk

factors, it should be taken into account that the risk may be superadditive. This may possibly result in a contraindication for HRT.

The risk of venous thromboembolic events occurring may be temporarily enhanced during prolonged immobilization, major surgery or after a serious accident. In women undergoing hormone replacement, the greatest attention must be paid to preventive measures in order to avoid venous thromboembolisms after surgery. Depending on the type of surgery and duration of immobilization, thought should be given to a temporary break in HRT treatment, in the case of elective surgery possibly several weeks (4-6 weeks) in advance. Treatment should only be resumed when the women is completely mobile again.

Dementia

In the Women's Health Initiative Memory Study (WHIMS), a randomized, placebo-controlled study subordinated to the WHI study, more than 2,000 women aged above 65 years (average age 71) received oral conjugated equine estrogens and medroxyprogesterone acetate and were monitored over an average period of 4 years.

In addition, 1,464 hysterectomized women aged between 65 and 79 were treated with oral conjugated equine estrogens alone and were monitored for an average of 5.2 years. Neither treatment with conjugated estrogens and medroxyprogesterone acetate nor with estrogen monotherapy showed any positive effect on cognitive function. The risk of any cerebral disturbance occurring (probably dementia) was actually higher (RR 2.05 [95% Cl 1.21-3.48] for the combined HRT. In absolute numbers this means an additional 23 cases per year per 10,000 women being treated.

Although it is still unclear to what extent the results of these studies may be extrapolated to a younger population or to HRT preparations with different active ingredients they should be taken into account by the doctor when judging the risk/benefit ratio of HRT.

Other precautionary measures

Estrogens may cause fluid retention. Patients with conditions that may worsen as a result (such as heart or kidney function disorders, asthma, epilepsy or migraine) should therefore be monitored carefully.

No clear association has been recorded to date between the use of HRT and the development of clinical hypertension. A slight increase in blood pressure has been seen in women on HRT, but a clinically significant increase is rare. If a continually enhanced blood pressure is ascertained under HRT, consideration should be given to the idea of discontinuing treatment.

Patients who take hypotensive medication at the same time as Progyluton should have their blood pressure checked on a regular basis.

An HRT may lead to an increase in triglyceride levels, which may increase the risk of pancreatitis in patients with preexisting hypertriglyceridemia. Therefore, the triglyceride levels should be monitored in such patients.

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Clinical studies have demonstrated an influence of HRT on peripheral insulin resistance and glucose tolerance. As a rule, however, it is not necessary to make any adjustments to antidiabetic therapy. Diabetics on HRT should have their blood sugar levels closely monitored.

Women with hepatic function disorders, including hyperbilirubinemia 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, hyperlipidaemia).

It is necessary for patients with a preexisting prolactinoma to be monitored closely by the doctor (this includes regular prolactin level determinations), since it has been reported that in isolated cases prolactinomas have increased in size under estrogen therapy.

Renally impaired patients or those with metabolic bone diseases accompanied by hypercalcemia should, as with any estrogen-containing preparation, only use Progyluton after a careful weighing up of the benefits and risks.

As a result of estrogen stimulation, some patients on HRT may suffer undesired side effects, such as unusually heavy bleeding. Frequent and persistent irregular bleeding is a sign of endometrial activity and must be clarified by appropriate diagnostic means in order to rule out organic diseases.

Uterine myomas may increase in size under estrogen therapy. If this is detected, therapy should be discontinued.

Should an endometriosis be reactivated under HRT it is recommended to discontinue this therapy.

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.

On occasions, chloasma may occur, particularly in women with a history of chloasma gravidarum. Women with a predisposition for chloasma should not expose themselves to the sun or other ultraviolet radiation during HRT.

In women with hereditary angioedema, any exogenous estrogens may trigger or exacerbate the 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 has no contraceptive effect. If necessary, nonhormonal contraceptive methods should be used.

Each Progyluton white coated tablet contains 46.220 mg lactose monohydrate. Each Progyluton light brown coated tablets contain 45.720mg lactose monohydrate. Each tablet contains 33.980 mg sucrose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicine.

4.5 Interactions with other medicinal products and other forms of interactions

In order to detect potential interactions, the summary of product characteristics of the concomitantly administered medicinal products should also be consulted.

Pharmacokinetic interactions

Influence of other medicinal products on the pharmacokinetics of Progyluton

Enzyme-inducing agents

An enhanced clearance of sex hormones owing to the induction of hepatic enzymes may lead to reduced plasma concentrations of estrogens and/or progestogens and thus impair the clinical efficacy as well as possibly cause bleeding irregularities. The same is true, for example, for barbiturates, bosentan, carbamazepine, felbamate, modafinil, oxcarbazepine, phenytoin, primidone, rifabutin, rifampicin and topiramate, as well as for medicinal products that contain St. John's wort (Hypericum perforatum). Enzyme induction can already be observed after a few days and can last for at least 4 or more weeks after discontinuation of these medicinal products. Maximum enzyme induction generally appears after a few weeks.

Enzyme inhibitors

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

Active substances with different influence on the clearance of sex hormones

Several inhibitors of HIV/HCV protease and of non-nucleoside reverse transcriptase can raise or lower the plasma concentrations of estrogen or progestogens if they are administered concomitantly with an HRT. These changes may be clinically relevant in some cases.

Enterohepatic circulation

In the case of concomitant short-term (up to 10 days) administration of antibiotics that do not exhibit any interactions with the CYP3A4 enzyme system, pharmacokinetic interactions are not expected. There is insufficient data available concerning possible interactions during longer-term comedication with antibiotics (e.g. for borreliosis or osteomyelitis). Reduction of the active substance levels due to an influence on the enterohepatic circulation cannot be ruled out here.

Influence of Progyluton on the pharmacokinetics of other medicinal products

Sex hormones may also influence the pharmacokinetics of other medicinal products. Correspondingly, their plasma concentrations can be either increased (e.g. ciclosporin) or reduced (e.g. lamotrigine, see below).

An interaction study with lamotrigine, which is an antiepileptic, and a combined oral contraceptive (30 μg ethinylestradiol/150 μg levonorgestrel) revealed a clinically relevant increase in lamotrigine clearance with a corresponding significant decrease in the lamotrigine

plasma level when these medicinal products were administered concomitantly. Such a decrease in the plasma concentrations may be accompanied by reduced seizure control. Adjustment of the lamotrigine dose may be necessary.

Other hormonal contraceptives or HRT preparations have not been investigated. However, it is expected that such preparations have a comparable interaction potential. If treatment with Progyluton is initiated in a patient who is taking lamotrigine, an adaptation of the lamotrigine dose may therefore be necessary, and the lamotrigine concentrations should be closely monitored at the beginning of the therapy.

Upon discontinuation of Progyluton, the lamotrigine levels may increase again, and so the patient should also be monitored in this phase and if necessary the lamotrigine dose should be reduced.

Sex hormones may also influence the effect of oral anticoagulants.

Interactions with unknown mechanism

In clinical studies where combined contraceptives containing ethinylestradiol were administered concomitantly with specific combinations (ombitasvir / paritaprevir / ritonavir used in the therapy of HCV infections with or without dasabuvir, glecaprevir/pibrentasvir; sofosbuvir/velpatasvir/voxilaprevir) , a clinically relevant increase in ALT (including cases of an increase to more than five times the upper limit of the normal range) occurred significantly more frequently compared with patients who were treated exclusively with the antiviral active substances. During administration of other estrogens (especially estradiol and estradiol valerate), on the other hand, the incidence of a transaminase elevation was not greater than in patients without estrogen therapy. Due to the limited number of women who were taking such other estrogen-containing medicinal products, however, caution is absolutely advised in the case of concomitant administration of estrogens with any of the above drug combinations.

4.6 Fertility, Pregnancy and lactation

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

There are, on the strength of animal experiments, signs of risks to the fetus. Most of the epidemiological studies conducted to date have failed to show any conclusive evidence of an embryotoxic or teratogenic effect, if estrogens or combinations of estrogens and progestogens were administered inadvertently during pregnancy.

During lactation, there is no indication for Progyluton.

The medicinal product must not be used during lactation, since milk production is reduced and the quality of the milk may change; also low concentrations of the substance can be detected in the milk.

4.7 Effect on ability to drive and use machines

No studies have carried out in this respect. Progyluton is not expected to influence the ability to drive or operate machines, cf. however the section “Undesirable effects”.

4.8 Undesirable effects

The serious undesirable effects linked to the use of an HRT are also described in the section “Special warnings and special precautions for use” (q.v.).

The following lists the undesirable effects by organ system and frequency, observed under HRT preparations. A connection with Progyluton cannot be corroborated, nor can it be ruled out.

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

Benign, malignant and unspecific growths (including cysts and polyps)

Uncommon: mammary carcinoma.

Unknown: endometrial carcinoma.

Diseases of the immune system

Uncommon: hypersensitivity reactions.

Metabolic and nutritional disorders

Common: weight gain.

Unknown: weight loss.

Psychiatric diseases

Common: mood swings, depression.

Uncommon: changes in libido*, nervousness.

Rare: anxiety.

* Both decreased and increased libido have been reported.

Diseases of the nervous system

Common: headache.

Uncommon: sleep disorders, dizziness, migraine.

Eye diseases

Uncommon: visual impairments.

Heart disease

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

Vascular disease

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

Diseases of the gastrointestinal tract

Common: flatulence, stomach pain, nausea, dyspepsia.

Uncommon: vomiting.

Liver and gallbladder disorders

Uncommon: abnormal liver function tests.

Very rare: cholestatic jaundice.

Unknown: cholelithiasis (and other gallbladder diseases).

Diseases of the skin and subcutaneous tissue

Common: skin rash, pruritus.

Uncommon: acne, hirsutism, alopecia, urticaria.

Unknown: chloasma, erythema nodosum, erythema multiforme, vascular purpura.

Skeletomuscular, connective tissue and bone diseases

Common: back pain.

Uncommon: muscle cramps.

Diseases of the sex organs and of the mammary glands

Very common: feeling of tightness in the breasts, breast pain, bleeding anomalies (menorrhagia, metrorrhagia, spotting, etc.)

Common: abdominal pain, vaginal discharge, increased size of uterine myomas, enlargement of the breasts.

Rare: dysmenorrhea, premenstrual syndrome.

Unknown: endometrial hyperplasia.

General diseases

Common: peripheral edema, asthenia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Owing to the low acute toxicity of the active substances estradiol valerate and norgestrel no acute intoxication risk is likely, even if a multiple of the therapeutically required dose is ingested by mistake on one occasion.

An acute overdose may be accompanied by headaches, nausea, vomiting, feeling of tightness in the chest and uterine bleeding.

With chronic overdosage an increase in undesirable effects and heightened risks as described in the section “Special warnings and special precautions for use” can be expected.

No specific antidote exists. Symptomatic treatment must be provided if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03FB01

Mode of action

Progyluton is a two-step HRT preparation for after the menopause and for regulating the cycle in younger women

Estradiol

After oral administration the active substance estradiol valerate is rapidly released. Estradiol, which is primarily produced by the ovarian follicle in women from the menarche to the menopause, is the most effective estrogen at the receptor level (e.g., uterus, vagina, urethra, breast, hypothalamus, pituitary, osteoblasts and liver).

In many women the failure of ovarian estrogen leads to vasomotor and thermoregulatory instability (hot flushes), disturbed sleep, depressive moods and an increasing atrophy of the urogenital system. These disturbances can be largely rectified by estrogen replacement. On the other hand, Progyluton can only improve depressive moods, if they occur in the context of vasomotor symptoms.

Estrogen replacement at doses that effect an improvement in the menopausal complaints also has a strong excitatory effect on mitosis and the proliferation of the endometrium. Estrogen monotherapy increases the incidence of endometrial hyperplasia and the risk of developing endometrial cancer. In Progyluton estradiol valerate is cyclically combined with norgestrel, thus largely obviating this risk.

Norgestrel

Norgestrel is a progestogen which in general mimics the biological effects of the endogenously produced progestogen progesterone: Progesterone affects all tissues that contain estrogen receptors, it induces protein synthesis and at the same time reduces the number of estrogen and progesterone receptors, thus limiting any excessive stimulation of growth in the target organs caused by the estrogen.

The main target organs of the progestogens include the uterus in which the secretory transformation of the endometrium proliferated under estrogen influence is induced by its effect. When the progestogen concentration falls, the endometrium previously proliferated by the estrogen is then shed.

The additional administration of a progestogen on 10 to 14 days (preferably 12) during each cycle together with a continuous estrogen therapy largely prevents the overstimulation of the endometrium, which would otherwise happen with an estrogen monotherapy. This considerably reduces the incidence of hyperplasia, which can lead to bleeding irregularities and to endometrial cancer.

Progyluton is especially suitable for women in the perimenopause: It overcomes the typical subjective complaints and regularizes the cycle.

At a dosage of 2 mg estradiol valerate has only a very small central inhibitory effect. As a result there is in general no ovulation inhibition during the administration of Progyluton, and the body’s own hormone production is scarcely impaired. For this reason the preparation may also be used in specific circumstances for stabilizing and regularizing the cycle in younger women (“Special warnings and special precautions for use”).

5.2 Pharmacokinetic properties

Estradiol valerate

Absorption

After oral administration, estradiol valerate is rapidly and completely absorbed. The steroid ester is split into estradiol and valeric acid as soon as it reaches the intestinal wall and during its first passage through the liver. Because of the first-pass metabolism, the bioavailability of estradiol is only approximately 3%.

As a rule, the maximum estradiol concentrations (approx. 30 pg/mL) in plasma are attained 4-9 hours after taking one tablet.

Between the treatment phase with estradiol valerate alone and that the treatment phase in combination with norgestrel, the estrogen levels show no relevant differences.

Compared with taking the tablet on an empty stomach, taking it with food has no influence on the bioavailability of estradiol.

Steady state

Estradiol serum levels have been observed to be roughly twice as high after repeated administration when compared to a single dose. On average, the steady state concentration is C_{min} 30 pg/mL and C_{max} 60 pg/mL.

Distribution

In plasma approx. 60 % of the estradiol is bound to albumin and just short of 40 % to SHBG. Only 1-1.5 % of the estradiol is freely available in the plasma.

The apparent distribution volume of estradiol after a single intravenous dose is approx. 1 L/kg.

Estradiol passes the placental barrier.

Only a very small amount of estradiol and its metabolites find their way into the mother's milk.

Metabolism

Following the ester splitting of estradiol valerate, an extensive metabolism of the estradiol, involving CYP3A4, takes place, producing primarily estrone, estriol and estrone sulfate, and this follows the biotransformation path of the endogenous estradiol. The main active metabolite, estrone, achieves plasma levels that are approximately 8 times higher compared with estradiol, and estrone sulfate achieves plasma levels that are around 150 times higher. The metabolic clearance rate for estradiol is about 10-30 mL/min/kg.

Elimination

Estradiol metabolites are conjugated to around 90 % with glucuronide or sulfate and are excreted via the urine with a half-life of approx. one day. Only approx. 10 % of the metabolites are excreted in the feces and are subject to an enterohepatic circulation.

2-3 days after therapy has stopped, the levels of estradiol return to those before therapy started.

Norgestrel

Absorption

Following oral administration, norgestrel is quickly and completely absorbed. The active component of the racemate norgestrel is levonorgestrel, which is fully bioavailable. As a rule

plasma levels of levonorgestrel peak at 7-8 ng/mL as early as 1-1.5 h after a single dose of Progyluton.

Steady state

After repeated administration, elevated trough levels of approximately 1 ng/mL were measured. In the case of administration of the estrogen-progestogen combination, however, the exposure (AUC) does not differ in a relevant manner between the steady state and a single dose.

Distribution

Only approximately 1.3% of the overall serum concentration of levonorgestrel is in the form of a free steroid, approximately 64% is bound specifically to SHBG and approximately 35% is bound nonspecifically to albumin. The relative proportions of free levonorgestrel, levonorgestrel bound to albumin and levonorgestrel bound to SHBG are heavily dependent on the concentration of SHBG in the plasma. The concentration of SHBG peaks at the end of the estrogen monophase of the Progyluton therapy cycle and then falls to a trough by the end of the combination phase. The estradiol-induced increase in SHBG concentration results in an increase in the proportion bound to SHBG and in a reduction in the free proportion.

Approximately 0.1% of the applied dose passes into the mother's 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

Elimination of levonorgestrel is in two stages. The clearance rate is roughly 1 mL/min/kg.

The metabolites are excreted with a half-life of approx. 1 day in roughly equal shares in the urine and bile.

Kinetics of special patient groups

Impaired kidney function: The pharmacokinetics of Progyluton in patients with renal insufficiency have not been investigated.

Impaired liver function: The pharmacokinetics of Progyluton in patients with hepatic insufficiency have not been investigated. However, it is known that the metabolic breakdown of estrogens and progestogens is slowed in the case of liver function disorders (see also "Warnings and precautions").

5.3 Preclinical safety data

Carcinogenicity

Preclinical trials with estradiol and combinations of estradiol with progestogens on repeated-dose toxicity, genotoxicity and carcinogenic potential failed to provide conclusive evidence of

any particular risk for humans, even though an enhanced carcinogenic risk was demonstrated in epidemiological studies as well as animal studies with estradiol.

Embryotoxicity/teratogenicity

Reproduction toxicology studies with levonorgestrel showed no teratogenic potential and no risk of virilizing female fetuses in connection with the partial androgenic effect of levonorgestrel in therapeutic doses. However, pregnancy is a contraindication for the use of Progyluton.

The serum levels of estradiol achieved when estradiol valerate is used are within the physiological range.

Mutagenicity

In-vitro and in-vivo studies with 17β-estradiol or with levonorgestrel (i.e. the pharmacologically active enantiomer of norgestrel) provided no evidence of any mutagenic potential.

Special notes

Influence on diagnostic methods

Sex hormones can impair the findings of certain laboratory tests, such as biochemical parameters of the liver, thyroid, adrenal and renal functions, plasma levels of binding proteins and lipid/lipoprotein fraction, parameters of carbohydrate metabolism, coagulation and fibrinolysis. In general, the changes remain within the reference range.

6. PHARMACEUTICAL PARTICULARS

6.1 list of exicipients

Lactose monohydrate, maize starch, polyvidone 25000, talc, magnesium stearate, sucrose, polyvidone 700000, macrogol 6000, calcium carbonate, glycerol 85%, titanium dioxide (E171), ferric oxide yellow (E172), ferric oxide red (E172) , montanglycol wax

6.2 Incompatabilitis

None known

6.3. Shelf-life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Keep out of reach of children.
Do not store above 25°C.

6.5 Nature and contents of container

Calendar pack containing 1 x 21 coated tablets (B)

7. Marketing authorization holder

Bayer Israel LTD, 36 Hacharash st., Hod Hasharon 4527702

8. Manufacturer

Bayer Weimar GMBH UND CO.KG, Dobereinerstrasse 20, Weimar 99427, Germany

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