MENARINI

Progynova® 1 mg and 2 mg

Film-Coated Tablets

1. NAME OF THE MEDICINAL PRODUCT

Progynova 1 mg coated tablets
Progynova 2 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each beige coated tablet contains estradiol valerate 1.0 mg

Each white coated tablet contains estradiol valerate 2.0 mg

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 natural menopause or castration.

Prevention of postmenopausal osteoporosis.

4.2 Dosage and method of administration

4.2.1 Method of administration

Oral use

4.2.2 Dosage regimen

- How to start Progynova

Hysterectomized patients may start at any time.

If the patient has an intact uterus and is still menstruating, a combination regimen with Progynova and a progestogen (see section 'Combination regimen') should begin within the first 5 days of menstruation.

Patients with amenorrhea or very infrequent periods or who are postmenopausal, may start a combination regimen (see section 'Combination regimen') at any time, provided pregnancy has been excluded.

Change from other HRT (cyclic, sequential, or continuous combined)

Women changing from other HRT should complete the current cycle of therapy before initiating Progynova therapy.

- Dosage

One beige Progynova tablet 1.0 mg (or one white Progynova tablet 2.0 mg) is taken daily.

- Administration

Each pack covers 28 days of treatment. Treatment is continuous HRT, which means that the next pack follows immediately without a break.

Combination regimen:

In women with intact uterus, the concomitant use of an appropriate progestogen is advised for 10-14 days every 4 weeks (continuous sequential or cyclic HRT) or with each tablet of estrogen (continuous combined HRT).

Adequate provision should be made by the physician to facilitate and assure a proper compliance of the patient with the recommended combined regimen.

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.

4.2.3 Additional information on special populations

4.2.3.1 Pediatric patients

Progynova 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

Progynova has not been specifically studied in patients with hepatic impairment. Progynova 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

Progynova 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
- Hypersensitivity to the active substance or to any of the excipients

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 hormone replacement therapy (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 post-traumatic 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 estrogen-only products.

Two large randomized trials with CEE alone or continuously combined with MPA showed risk estimates of 0.77 (95% confidence interval (CI): 0.59-1.01) or 1.24 (95%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 the one contained in Progynova. In isolated cases, these tumors led to life-threatening 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.

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 whilst 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 Progynova

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. 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.

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

4.6.1 Pregnancy

Progynova must not be used during pregnancy and lactation. (see section 'Contraindications'). If pregnancy occurs during medication with Progynova, treatment must 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 Progynova.

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

The table below reports undesirable effects,that have been reported in users of hormone replacement therapy (HRT) by MedDRA system organ classes (MedDRA SOCs).

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare <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	Breast pain, Breast tenderness	Dysmenorrhea, Vaginal discharge, Premenstrual-like syndrome, Breast enlargement
General disorders and administration site conditions		Edema	Fatigue

The most appropriate MedDRA (version 8.1) term is used to describe a certain reaction and its synonyms and related conditions.

4.8.3 Description of selected adverse reactions

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

Pharmacotherapeutic group: Natural and semisynthetic estrogens, plain

ATC Code: G03CA03

Progynova contains the estrogen estradiol valerate, a prodrug of the natural human 17ß-estradiol.

Ovulation is not inhibited during the use of Progynova, and the endogenous production of hormones is hardly affected.

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

HRT with an adequate estrogen dosage like in Progynova reduces bone resorption and retards or halts postmenopausal bone loss. 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.

The addition of a progestogen to an estrogen replacement regimen like Progynova for at least 10 days per cycle is recommended in women with an intact uterus. It reduces the risk of endometrial hyperplasia and the attendant risk of adenocarcinoma in these women. 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 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.

5.2.2 Distribution

Maximum concentrations of estradiol in serum of approx. 15 pg/ml (or 30 pg/ml) are generally expected between 4 - 9 hours after tablet intake. Within 24 hours after tablet intake, serum levels of estradiol are expected to decline to concentrations of about 8 pg/ml (or 15 pg/ml). Estradiol binds to albumin and the sex hormone binding globulin (SHBG). 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.

5.2.3 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.

5.2.4 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.

5.2.5 Steady-state conditions

In relation to the single dose, approximately two times higher serum levels of estradiol are expected after multiple administration. On average, the concentration of estradiol varies between 15 (or 30 pg/ml) (minimum levels) and 30 (or 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, pre-treatment levels of estradiol and estrone are reached within 2-3 days.

5.3 Preclinical safety data

The toxicity profile of estradiol is well known. There are no preclinical data of relevance to the prescriber that are additional to those already included in other sections.

6. PHARMACEUTICAL PARTICULARS

List of excipients

Tablet core 1mg and 2mg tablet:

Lactose monohydrate
maize starch
polyvidone 25 000
talc
magnesium stearate

Sugar-coating:

1mg Tablet:

sucrose
polyvidone 700 000
Macrogol 6000
calcium carbonate
glycerol 85 %
titanium dioxide
ferric oxide pigment, yellow
montanglycol wax
talc

2mg Tablet:

sucrose
polyvidone 700 000
Macrogol 6000
calcium carbonate
montanglycol wax
talc

Nature and contents of container

Progynova 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 28 tablets

Storage Conditions

Store below 30°C

Manufacturer

Bayer Weimar GmbH und Co.KG
Doebereiner Str. 20
99427 Weimar
Germany

Date of Revision of Text

January 2026