## 1. NAME OF THE MEDICINAL PRODUCT

Progynova 1mg
Progynova 2mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each beige sugar-coated tablet contains estradiol valerate 1.0 mg.
Each white sugar-coated tablet contains estradiol valerate 2.0 mg

## 3. PHARMACEUTICAL FORM

Sugar-coated tablets

## 4. CLINICAL PARTICULARS

### 4.1 Indications

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

Hormonal contraception should be stopped when HRT is started and the patient should be advised to take non-hormonal contraceptive precautions, if required.

#### 4.2.3

**How to start Progynova**

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 post-menopausal, may start a combination regimen (see section “Combination regimen”) at any time, provided pregnancy has been excluded.

Estrogen with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual women.

**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 tablet Progynova 1.0mg tablet (or one white tablet Progynova 2.0mg tablet ) is taken daily. –

**Administration**

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

The tablets are to be swallowed whole with some liquid.

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

**Combination regimen**
In women with intact uterus, the concomitant use of an appropriate progestogen is advised for 10-14 days every 4 weeks (sequentially combined 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.

***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 Children and adolescents
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. In women aged 65 years or older, see section 4.4, “Special warnings and precautions for use”.

4.2.3.3 Patients with hepatic impairment
Progynova has not been specifically studied in hepatic-impaired patients. Progynova is contraindicated in women with severe hepatic diseases (see section “Contraindications”).

4.2.3.4 Patients with renal impairment
Progynova has not been specifically studied in renally-impaired patients. Available data does not suggest a need for dosage adjustment in this patient population.
Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

**4.3 Contraindication**

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 tumours (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 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 cerebrosvascular occlusion.
- Recurrence of cholestatic jaundice or cholestatic pruritus which occurred first during pregnancy or previous 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 increase 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.

HRT should not be initiated or continued to prevent coronary heart disease and the benefits and risks of HRT must be carefully weighed when considering use in women without menopausal symptoms or for long-term use.

The WHI Estrogen mono (E mono) study recruited 10,739 postmenopausal women in the USA. Participants received conjugated equine estrogens, 0.625mg/day, in 1 tablet (marketed in the USA as Premarin), or placebo. The 9-year study was designed primarily to assess whether long-term use of this HRT preparation reduces the risk of coronary heart disease (CHD) in postmenopausal women. It was stopped early (after an average of 6.8 years) because of an increased risk of stroke in women using the drug.

The results of the study suggest that for every 10,000 women treated with the HRT preparation, per year, an extra 12 women developed stroke, an extra 3 had a serious blood clot in the lungs, and an extra 1 developed colorectal cancer. In contrast, 5 fewer women developed coronary heart disease, 7 fewer breast cancer, 6 fewer suffered a hip fracture, The study concluded that the burden of incident disease events was equivalent in the CEE and placebo groups over an average of 6.8 years, indicating no overall benefit. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.

• Venous thromboembolism
Both randomized-controlled and epidemiological studies have suggested that hormone replacement therapy (HRT) may be associated with an increased relative risk (RR) of developing venous thromboembolism (VTE), i.e. deep venous thrombosis or pulmonary embolism. Risk/benefit 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 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.

Tumours

• 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.

Two large, randomised 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.

Similar increases in breast cancer diagnosis are observed, e.g. with delay of natural menopause, alcohol intake, or adiposity.

The excess risk disappears 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 tumour
In rare cases, benign and, even more rarely, malignant liver have been observed after the use of hormonal substances such as the one contained in Progynova. In isolated cases, these tumours led to life-threatening intra-abdominal hemorrhage. A hepatic tumour should be considered in the differential diagnosis, if upper abdominal pain, enlarged liver or signs of intra-abdominal hemorrhage occur.

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

Prolactinoma should be ruled out before treatment. Close medical supervision (including periodic measurement of prolactin levels) is necessary during HRT treatment if the patient has a high risk of developing 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 extrogens may induce or exacerbate symptoms of angioedema.

**4.4.1 Medical examination/consultation**

A complete medical history should be taken and a physical examination should be conducted prior to the initiation or reinstitution of HRT, guided by the contraindications (see Section “Contraindications”) and warnings (see Section “Special warnings and precautions for use”) and should be repeated periodically. The frequency and nature of these examinations should be based on established practice guidelines and be adapted to the individual woman, but should generally include pelvic organs, including routine cervical cytology, abdomen, breasts and blood pressure.

**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***

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 with the normal laboratory range.

**4.6 Pregnancy and lactation**

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

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**

In addition to the adverse effects listed in the sections “Contraindications” and “Special warnings and special precautions for use”, the following undesirable effects have been reported in users of different oral HRT preparations by MedDRA System Organ Classes (MedDRA SOCs, version 8.1).

- Immune system disorders

Hypersensitivity reaction

- Metabolism and nutrition disorders

Weight increase, weight decrease

- Psychiatric disorders

Depressed mood, anxiety, libido decreased, libido increased

- Eye disorders

Visual disturbances, contact lens intolerance

- Cardiac disorders

Palpitations

- Musculoskeletal and connective tissue disorders

Muscle cramps

- Reproductive system and breast disorders

Uterine/vaginal bleeding including spotting, dysmenorrhoea, vaginal discharge, premenstrual-like syndrome, breast pain, breast tenderness, breast enlargement

- Gastrointestinal disorders

Dyspepsia, bloating, nausea, vomiting, abdominal pain, increased appetite

- Skin and subcutaneous tissue disorders

Rashes, various skin disorders (including pruritus, eczema, urticaria, acne, hirsutism, hair loss, erythema nodosum)

- Nervous system disorders

Headache, migraine, dizziness

- General disorders and administration site conditions

Edema, fatigue

**4.8.2 Description of selected adverse reactions**

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema (see section 4.4, “Special Warnings and 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.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

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.

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

- 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.

- 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.

- 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.

- 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.

- 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Tablet core 1mg and 2mg tablet:**
Lactose monohydrate
Maize Starch
Magnesium stearate
Povidone 25

Talc

**Sugar-coating:**

**1mg Tablet:**
Calcium carbonate
Ferric oxide yellow
Glycerol 85%
Glycol montanate
Macrogol 6000
Povidone 90
Sucrose
Talc
Titanium dioxide

**2mg Tablet:**
Calcium carbonate
Glycol montanate
Macrogol 6000
Povidone 90
Sucrose
Talc

### 6.2 Shelf life

Please refer to labels.

### 6.3 Special precautions for storage

Store all drugs properly and keep them out of reach of children
Store below 30°C.

### 6.4 Presentation

28 tablets of Progynova 2mg
28 tablets of Progynova 1mg
Not all presentations are available.

### 6.5 Nature and contents of container

Progynova 28 tablets are contained in blister packs consisting of transparent films made of polyvinyl chloride and metallic foils made of aluminum (mat side hot sealable).

### 6.6 Manufacturer

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

### Date of Revision

14 December 2021

If you would like to report a side effect for any Bayer Pharmaceutical or Consumer Health product, you can do it easily using our online reporting portal: https://safetrack-public.bayer.com/ or scan the QR code available below. Please also remember to seek medical advice directly from your doctor or pharmacist.

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