

DATA SHEET

PROGYNOVA®

oestradiol valerate tablets

Presentation

PROGYNOVA 1 mg: The memo-pack holds 28 beige, biconvex, round tablets, each containing 1.0 mg oestradiol valerate.

PROGYNOVA 2 mg: The memo-pack holds 28 light blue, biconvex, round tablets, each containing 2.0 mg oestradiol valerate.

All tablets have a lustrous sugar coating and are approximately 7mm in diameter.

Indications

Hormone replacement therapy (HRT) for the treatment of signs and symptoms of oestrogen deficiency due to the menopause (whether natural or surgically induced).

Prevention of postmenopausal osteoporosis.

Dosage and Administration

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

Hysterectomised patients may start at any time.

If the patient is still menstruating and has an intact uterus, a combination regimen of PROGYNOVA and a progestogen should begin within the first 5 days of menstruation (see below for combination regimen). Patients whose periods are very infrequent or with amenorrhoea or who are postmenopausal may start at any time, provided pregnancy has been excluded.

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

Continuous Regimen

It does not matter at what time of day the patient takes her tablet(s), but once she has selected a particular time, she should keep to it every day. If she forgets to take a tablet at the usual time, she may take it within the following 12 to 24 hours. If the treatment is discontinued for longer, irregular bleeding may occur.

One tablet is taken daily (either one beige 1 mg tablet or one blue 2 mg tablet).

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.

Combination Regimen

In women with an 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 oestrogen (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.

It does not matter at what time of the day the patient takes her tablet, but once she has selected a particular time, she should keep to it every day. If she forgets to take a tablet at the usual time, she may take it within the following 12 to 24 hours. If the treatment is discontinued for longer, irregular bleeding may occur.

Contraindications

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

- Pregnancy or 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 (myocardial infarction, stroke) or a recent history of these conditions
- Active deep venous thrombosis, thromboembolic disorders, thrombophlebitis, or a documented history of these conditions
- A high risk of venous or arterial thrombosis
- Hereditary or acquired predisposition to venous thrombosis (e.g. antithrombin III deficiency)
- Severe hypertriglyceridemia
- Hypersensitivity to any of the components of PROGYNOVA

Warnings and Precautions

PROGYNOVA cannot be used as a contraceptive.

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

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.

If contraception is required, non-hormonal methods should be used (with the exception of the rhythm and temperature methods). If there is a chance that pregnancy has occurred, tablet taking must be interrupted until it has been ruled out.

Oestrogens with or without progestogens should not be used for the long-term maintenance of general health, including the primary prevention of cardiovascular disease as the risks of long-term treatment with HRT in most circumstances, outweigh the benefits. The Women's Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in postmenopausal women during five years of treatment with conjugated equine oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to the placebo (see table below).

The WHI study was designed to investigate the efficacy and safety of long-term HRT in preventing coronary heart disease in healthy postmenopausal with an intact uterus. A total of 8506 women received HRT and 8102 women received placebo for an average of 5.2 years.

Table: Summary of the incidence of adverse events described in the WHI study

Adverse Event	Relative Risk of HRT vs placebo at 5.2 years (95% CI)	Change in number of adverse events per 10,000 women in one year
Breast cancer	1.26 (1.00-1.59)	8 extra
Heart disease	1.29 (1.02-1.63)	7 extra
Stroke	1.41 (1.07-1.85)	8 extra
Pulmonary embolism	2.13 (1.39-3.25)	8 extra
Myocardial infarction	1.32 (1.02-1.72)	*
Deep vein thrombosis	2.07 (1.49-2.87)	*
Colorectal cancer	0.63 (0.43-0.92)	6 fewer
Hip fracture	0.66 (0.45-0.98)	5 fewer

* Information not available

Other doses of conjugated oestrogens and medroxyprogesterone acetate and other combinations of oestrogens and progestogens were not studied in the Women's Health Initiative (WHI) and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, oestrogens and progestogens should be prescribed at the lowest effective doses and for the shortest duration (generally not longer than 3-4 years), consistent with the treatment goals and risks for the individual woman.

All prospective and current users of HRT should be advised of the risks and benefits of oestrogens and progestogens and the need for treatment with HRT should be reviewed on a yearly basis.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before PROGYNOVA is started or continued.

Venous Thromboembolism

Both randomised-controlled and epidemiological studies have suggested an association between the use of HRT and an increased relative risk (RR) of venous thromboembolism (VTE), i.e. deep venous thrombosis or pulmonary embolism. PROGYNOVA is contraindicated in women with a history of or predisposition to thromboembolic disorders.

Treatment should be stopped at once if there are symptoms of a thrombotic event or suspicion thereof. Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very

marked numbness suddenly affecting one side or one part of the body; motor disturbances; “acute” abdomen.

Generally recognised 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 obesity (body mass index >30 kg/m²). The risk of VTE also increases with age. Extensive varicose veins and superficial thrombophlebitis may have a role in VTE. The risk of VTE may be temporarily increased with prolonged immobilisation, major elective or post-traumatic surgery, or major trauma. Depending on the nature of the event and the duration of the immobilisation, consideration should be given to a temporary discontinuation of HRT.

Arterial Thromboembolism

Two large clinical trials with continuous combined conjugated oestrogens (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 extend to other HRT products or non-oral routes of administration.

Gall Bladder Disease

Oestrogens are known to increase the lithogenicity of the bile. Some women are predisposed to gallbladder disease during oestrogen 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.

HRT and Cancer

Suspected prolactinoma should be ruled out before starting PROGYNOVA treatment.

Endometrial Cancer

Prolonged monotherapy with oestrogens increases the risk of endometrial hyperplasia and carcinoma in postmenopausal women. Oestrogen or oestrogenic compounds must not be used alone as hormone replacement therapy in women who have not had a hysterectomy. Close clinical surveillance of all women taking oestrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. Studies have found that protection from this effect is achieved with 10 or more days of progestogen therapy per month.

Ovarian Cancer

Ovarian cancer is less prevalent than breast 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 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).

Breast Cancer

Clinical and observational studies have reported an increased risk of having breast cancer diagnosed in women who have used HRT for several years. The findings may be due to an earlier diagnosis, growth promoting effects on pre-existing tumours, or a combination of both. 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 (by 2.3% per year of use) and may be lower or possibly neutral with oestrogen-only products. This is comparable to the increased risk observed in women with a delayed menopause. 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% 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 increased risk gradually disappears during the course of the first 5 years after cessation of HRT. HRT increases the density of mammographic images which may adversely affect the radiological detection of breast cancer in some case.

Liver Tumour

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

Other Conditions

Non-severe disturbances of liver function, including hyperbilirubinaemias 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.

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, although clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops, withdrawal of HRT may be considered.

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

PROGYNOVA. However, diabetic women should be carefully monitored while taking PROGYNOVA.

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

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

Should endometriosis be reactivated during treatment with PROGYNOVA, discontinuation of therapy is recommended.

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

As oestradiol can reduce urinary excretion of calcium, serum calcium levels should be carefully monitored in patients with pre-existing hypercalcaemia.

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 should be carefully monitored while taking PROGYNOVA: epilepsy, benign breast disease, asthma, migraine, porphyria, otosclerosis, systemic lupus erythematosus and chorea minor.

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

Medical Examination/Consultation

A complete medical history should be taken and a physical examination should be conducted prior to the initiation or reinstatement of treatment with PROGYNOVA, guided by the CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections, 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.

Use in Pregnancy

The use of PROGYNOVA is contraindicated during pregnancy. If pregnancy occurs during treatment with PROGYNOVA, treatment must be discontinued immediately.

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used sex hormones prior to pregnancy, nor a teratogenic effect when sex hormones were taken inadvertently during early pregnancy (see Contraindications).

Use in Lactation

The use of PROGYNOVA is contraindicated during lactation. Small amounts of sex hormones may be excreted in human milk.

Paediatric Use

PROGYNOVA is not indicated for use in children and adolescents.

Use in the Elderly

There are no data suggesting a need for dosage adjustment in elderly patients. In women aged 65 years or older, see WARNINGS AND PRECAUTIONS.

Patients with Hepatic Impairment

PROGYNOVA has not been studied in patients with hepatic impairment. PROGYNOVA is contraindicated in women with severe hepatic disease (see CONTRAINDICATIONS).

Patients with Renal Impairment

PROGYNOVA has not been studied in renally impaired patients. Available data does not suggest a need for dosage adjustment in this patient population.

PRECLINICAL SAFETY DATA

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

Carcinogenicity

Animal toxicity studies with repeated administration, including tumourigenicity studies, did not suggest a particular risk related to use in humans. However, it should be borne in mind that sex steroids might stimulate the growth of certain hormone-dependent tissues and tumours.

Mutagenicity

In vitro and *in vivo* studies with 17 β -estradioloestradiol gave no indications of a mutagenic potential.

Embryotoxicity/Teratogenicity

Reproductive toxicity studies with oestradiol valerate did not indicate a teratogenic potential. As no non-physiological plasma concentrations of oestradiol are produced by administration of oestradiol valerate, this preparation does not present a risk to the foetus.

Adverse Effects

Serious undesirable effects of PROGYNOVA have been referred to in the WARNINGS AND PRECAUTIONS sections.

In addition, the following undesirable effects have been reported in users of HRT, such as PROGYNOVA, by MedDRA system organ classes (MedDRA SOCs).

System Organ Class	Common (≥1/100, <1/100)	Uncommon (≥1/1000, <1/100)	Rare (<1/1000)
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	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	Dysmenorrhoea, Vaginal discharge, Premenstrual-like syndrome, Breast enlargement
General disorders and administration site conditions		Oedema	Fatigue

In women with hereditary angioedema, oestrogens may induce or exacerbate symptoms of angioedema.

Oestrogen-only and combined oestrogen-progestogen 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 WARNINGS AND PRECAUTIONS).

Interactions

The Data Sheet of concomitant medicines should be consulted to identify potential interactions.

Effects of other medicines 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 oestrogen. 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 oestrogen.

Substances that undergo substantial conjugation (e.g. paracetamol) may increase the bioavailability of oestradiol 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 oestradiol levels.

Effect on 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.

Overdosage

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.

Symptoms

Nausea, vomiting, withdrawal bleeding may occur in some women.

Treatment

There are no antidotes and treatment should be symptomatic.

Further Information

PHARMACODYNAMICS

PROGYNOVA contains the oestrogen oestradiol valerate, a prodrug of the natural human 17 β -oestradiol.

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 oestradiol 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.

HRT with an adequate oestrogen dosage as 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.

The addition of a progestogen to an oestrogen 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 oestrogen replacement regimen has not been shown to interfere with the efficacy of oestrogen for its approved indications.

PHARMACOKINETICS

Absorption

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

Distribution

Maximum concentrations of oestradiol in serum of about 15 pg/mL (or 30 pg/mL in the case of PROGYNOVA 2mg) are generally reached between 4 - 9 hours after tablet intake. Within 24 hours after tablet intake, serum levels of oestradiol are expected to decline to concentrations of about 8 pg/mL (or 15 pg/mL). Oestradiol binds to albumin and the sex hormone binding globulin (SHBG). The unbound fraction of oestradiol 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 oestradiol after single intravenous administration is about 1 L/kg.

Metabolism

After the ester cleavage of the exogenously administered oestradiol valerate, the metabolism of the medicine follows the biotransformation pathways of endogenous oestradiol. Oestradiol is mainly metabolised in the liver but also extrahepatically, e.g. in gut, kidney, skeletal muscles and target organs. These processes involve the formation of oestrone, oestriol, catecholestrogens and sulphate and glucuronide conjugates of these compounds, which are all distinctly less oestrogenic or even nonestrogenic.

Elimination

The total serum clearance of oestradiol following single intravenous administration shows high variability in the range of 10 - 30 mL/min/kg. A certain proportion of oestradiol metabolites are excreted in the bile and undergo enterohepatic circulation. Ultimately oestradiol metabolites are mainly excreted as sulphates and glucuronides with the urine.

Steady-State Conditions

After multiple administration, serum levels of oestradiol are about twice as high as those obtained after a single dose. On average, the concentration of oestradiol varies between 15 and 30 pg/mL for PROGYNOVA 1 mg strength and between 30 and 60 pg/mL for PROGYNOVA 2 mg. Oestrone, a less oestrogenic metabolite, reaches about 8 times higher concentrations in serum, and oestrone sulphate about 150 times higher concentrations. After stopping the treatment, pre-treatment levels of oestradiol and oestrone are reached within 2 - 3 days.

LIST OF EXCIPIENTS

PROGYNOVA 1 mg contains:

Lactose monohydrate, maize starch, polyvidone 25 000, purified talc, magnesium stearate, sucrose, polyvidone 700 000, macrogol 6000, calcium carbonate, glycerol 85%, titanium dioxide, ferric oxide pigment (yellow), montanglycol wax

PROGYNOVA 2 mg contains:

Lactose monohydrate, maize starch, polyvidone 25 000, purified talc, magnesium stearate, sucrose, polyvidone 700 000, macrogol 6000, calcium carbonate, glycerol 85%, titanium dioxide, indigo carmine lake, montanglycol wax

Pharmaceutical Precautions

STORAGE

Progynova 1 mg: Store below 30°C.

Progynova 2 mg: Store below 25°C.

INSTRUCTIONS FOR USE/HANDLING

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

Package Quantities

PROGYNOVA tablets are contained in blister packs consisting of transparent film made of polyvinyl chloride and metallic foil made of aluminium (mat side hot sealable).

PROGYNOVA is available in package sizes of 1, 2 or 3 x 28 tablets.

Not all pack sizes may be marketed.

Medicine Classification

Prescription Medicine

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