PRODUCT INFORMATION

PROGYNOVA®

WARNING

Oestrogens with or without progestogens should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated oestrogens (0.625 mg) relative to placebo (see CLINICAL TRIALS and PRECAUTIONS).

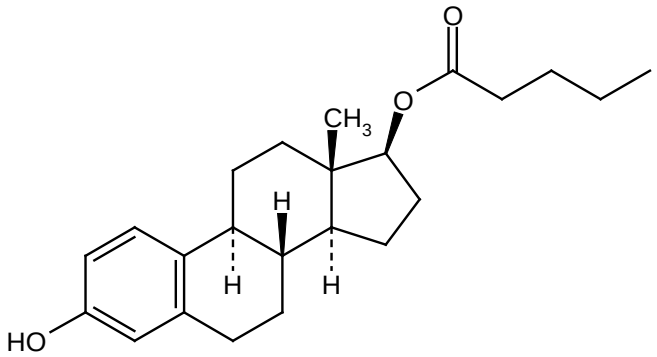
The WHI study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see CLINICAL TRIALS and PRECAUTIONS).

The Women's Health Initiative Memory Study (WHIMS), a sub-study of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 to 5.2 years of treatment with conjugated oestrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (see CLINICAL TRIALS and PRECAUTIONS).

Other doses of conjugated oestrogens and medroxyprogesterone acetate, and other combinations and dosage forms of oestrogens and progestogens were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, oestrogens 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 woman.

NAME OF THE MEDICINE

PROGYNOVA is the trade name for yellow coloured tablets that contain 1 mg oestradiol valerate or blue coloured tablets that contain 2 mg oestradiol valerate.



Chemical name:	1,3,5(10)-Estratriene-3,17β-diol-17-valerate
Molecular formula:	$C_{23}H_{32}O_3$
Molecular weight:	356.5
CAS No. :	979-32-8

DESCRIPTION

Oestradiol valerate exists as white to yellowish-white crystals or crystalline powder. The substance is freely soluble in acetone and dichloromethane, soluble in ethanol, methanol, dioxane and diethylether, very slightly soluble in n-hexane and practically insoluble in petroleum ether and water. The melting point is 143 to 150^{o}C.

Excipients 1 mg tablets: Lactose, maize starch, povidone 25000, magnesium stearate, purified talc, sucrose, povidone 700000, macrogol 6000, calcium carbonate, glycerol, titanium dioxide, iron oxide yellow and glycol montanate.

Excipients 2 mg tablets: Lactose, maize starch, povidone 25000, magnesium stearate, purified talc, sucrose, povidone 700000, macrogol 6000, calcium carbonate, glycerol, titanium dioxide, indigo carmine and glycol montanate.

PHARMACOLOGY

Pharmacodynamics

PROGYNOVA contains oestradiol valerate which is a prodrug of the natural human 17β-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, dysparenuria 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 oestradiol deficiency in the postmenopausal woman.

HRT 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.

During oestrogen replacement therapy, the addition of a progestogen 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.

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 sulfate. About 3% of oestradiol becomes bioavailable after oral administration of oestradiol valerate. Food does not appear to affect the bioavailability of oestradiol.

Distribution

Maximum concentrations of oestradiol in serum of approximately 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 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 drug follows the biotransformation pathways of endogenous oestradiol. Oestradiol is mainly metabolised in the liver but also extrahepatically e.g. in the gut, kidney, skeletal muscles and target organs. These processes involve the formation of oestrone, oestriol, catecholestrogens and sulfate and glucuronide conjugates of these compounds, which are all distinctly less oestrogenic or even nonoestrogenic.

There is a dynamic equilibrium between oestradiol, oestrone and oestrone-sulfate due to involvement of various enzymes including dehydrogenases, sulfotransferases, aryl sulfatases and glucuronosyltransferases and glucuronidases. Oxidation of oestrone and oestradiol involves cytochrome P450 isoforms, mainly CYP1A2, CYP1A1 (extra hepatic), CYP3A4, CYP3A5, and CYP1B1 and CYP2C9 (see INTERACTIONS WITH OTHER MEDICINES).

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 a so-called enterohepatic circulation. Ultimately oestradiol metabolites are mainly excreted as sulfates and glucuronides with the urine.

Steady-state conditions

Compared to the single dose, approximately two times higher serum levels of oestradiol are observed after multiple administration. On average, the concentration of oestradiol varies between 15 (pg/mL (or 30 pg/mL) (minimum levels) and 30 pg/mL (or 60 pg/mL) (maximum levels). Oestrone, as a less oestrogenic metabolite, reaches about 8-times higher concentrations in serum, oestrone sulfate reaches approximately 150-times higher concentrations. After stopping the treatment, pre-treatment levels of oestradiol and oestrone are reached within 2-3 days.

CLINICAL TRIALS

Women's Health Initiative Studies (WHI)

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of 0.625 mg conjugated oestrogens (CE) per day alone or the use of 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The oestrogen alone substudy was stopped early because an increased risk of stroke was observed and it was deemed that no further information would be obtained regarding the risks and benefits of oestrogen alone in predetermined primary endpoints. Results of the oestrogen alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3% White, 15% Black, 6.1% Hispanic), after an average follow-up of 6.8 years are presented in Table 1 below.

Table 1. Relative and Absolute Risk seen in the Oestrogen Alone Substudy of WHI[a]

Event[c]	Relative Risk* CE vs Placebo at 6.8 Years (95% CI)	Placebo n = 5429	CE n = 5310
		Absolute Risk per 10,000 Women-years	
CHD events	0.91 (0.75-1.12)	54	49
Non-fatal MI	*0.89 (0.70-1.12)*	*41*	*37*
CHD death	*0.94 (0.65-1.36)*	*16*	*15*
Invasive breast cancer	0.77 (0.59-1.01)	33	26
Stroke	1.39 (1.10-1.77)	32	44
Pulmonary embolism	1.34 (0.87-2.06)	10	13
Colorectal cancer	1.08 (0.75-1.55)	16	17
Hip fracture	0.61 (0.41-0.91)	17	11
Death due to other causes than the events above	1.08 (0.88-1.32)	50	53
Global Index[b]	1.01 (0.91-1.12)	190	192
Deep vein thrombosis[c]	1.47 (1.04-2.08)	15	21
Vertebral fractures[c]	0.62 (0.42-0.93)	17	11
Total fractures[c]	0.70 (0.63-0.79)	195	139

a: adapted from JAMA, 2004; 291:1701-1712
b: a subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
c: not included in Global Index
* nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE alone were 12 more strokes while the absolute risk reduction per 10,000 women-years was 6 fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant 2 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality (see BOXED WARNING and PRECAUTIONS).

The oestrogen plus progestogen substudy was also stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results of the oestrogen plus progestogen substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 2 below.

Table 2. Relative and Absolute Risk seen in the Oestrogen Plus Progestogen Substudy of WHI[a]

Event[c]	Relative Risk CE/MPA vs Placebo at 5.2 Years (95% CI*)	Placebo n = 8102	CE/MPA n = 8506
		Absolute Risk per 10,000 Women-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index [c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis[d]	2.07 (1.49-2.87)	13	26
Vertebral fractures[d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures[d]	0.77 (0.69-0.86)	170	131

a: adapted from JAMA, 2002; 288:321-333
b: includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
c: a subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
d: not included in Global Index
* nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

For those outcomes included in the WHI "global index," the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality (see BOXED WARNING and PRECAUTIONS).

Women's Health Initiative Memory Study

The oestrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45% were age 65 to 69 years, 36% were 70 to 74 years, and 19% were 75 years of age and older) to evaluate the effects of 0.625 mg conjugated oestrogens on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the oestrogen alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the oestrogen alone group was 1.49 (95% CI, 0.83 to 2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women (see BOXED WARNING and PRECAUTIONS, Dementia and Use in the Elderly).

The oestrogen plus progestogen WHIMS substudy enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the oestrogen/progestogen group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women (see BOXED WARNING and PRECAUTIONS, Dementia and Use in the Elderly).

INDICATIONS

Short term treatment of climacteric complaints after the cessation of monthly bleeding, or deficiency symptoms after oophorectomy or radiological castration for non-carcinomatous diseases, such as hot flushes, outbreaks of sweat, sleep disturbances, depressive moods, irritability, headaches, dizziness.

PROGYNOVA also has a favourable influence on bladder irritation (a not infrequent occurrence in the climacteric), signs of cutaneous and mucosal involution (particularly in the genital region) which normally occur with advancing age.

CONTRAINDICATIONS

HRT should not be started in the presence of any of the conditions listed below. Should any of the following 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 vein thrombosis, thromboembolic disorders, or a documented history of these conditions
- A high risk of venous or arterial thrombosis
- Severe hypertriglyceridemia
- Idiopathic cholestatic jaundice of pregnancy or jaundice with prior combined oral contraceptive use or combined HRT use
- Otosclerosis with deterioration during pregnancy
- Severe diabetes with vascular changes
- Known hypersensitivity to any of the components of PROGYNOVA

PRECAUTIONS

The benefits and risks of HRT must be carefully weighed, including consideration of the emergence of risks as therapy continues. Oestrogens with or without progestagens should be prescribed at the lowest effective doses and for the shortest duration consistent with the treatment goal and risks for the individual women.

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

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 increase risk may be greater than a simple cumulative risk of the factor. HRT should not be prescribed in case of a negative risk benefit assessment.

1. Cardiovascular Disorders

Oestrogen and oestrogen/progestogen therapy have been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, oestrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Coronary heart disease and stroke.
In the oestrogen alone substudy of the Women's Health Initiative (WHI) study, an increased risk of stroke was observed in women receiving 0.625 mg conjugated oestrogens per day compared to women receiving placebo (44 vs 32 per 10,000 women-years). The increase in risk was observed in year one and persisted (see CLINICAL TRIALS).

In the oestrogen plus progestogen substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate (CE/MPA) per day compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same oestrogen plus progestogen substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Oestrogen/progestin Replacement Study; HERS) treatment with 0.625 mg conjugated oestrogen plus 2.5 mg medroxyprogesterone acetate per day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate group and the placebo group in HERS, HERS II, and overall.

b. Venous thromboembolism (VTE)
In the oestrogen alone substudy of the Women's Health Initiative (WHI) study, an increased risk of deep vein thrombosis was observed in women receiving receiving 0.625 mg conjugated oestrogens compared to placebo (21 vs 15 per 10,000 women-years). The increase in VTE risk was observed during the first year (see CLINICAL TRIALS).

In the oestrogen plus progestogen substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving with 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, oestrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilisation.

2. Malignant Neoplasms

a. Endometrial cancer
The use of unopposed oestrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed oestrogen users with an intact uterus is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on oestrogen dose. Most studies show no significant increased risk associated with the use of oestrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after oestrogen therapy is discontinued.

Clinical surveillance of all women taking oestrogen/progestogen combinations 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. There is no evidence that the use of natural oestrogens results in a different endometrial risk profile than synthetic oestrogens of equivalent oestrogen dose. Adding a progestogen to postmenopausal oestrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Addition of a progestogen when a woman has not had a hysterectomy
Studies of the addition of a progestogen for 10 or more days of a cycle of oestrogen administration, or daily with oestrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestogens with oestrogens compared to oestrogen-alone regimens. These include: a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance.

b. Breast cancer
In some studies, the use of oestrogens and progestogens by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) trial of oestrogen plus progestogen (see CLINICAL TRIALS). The results from observational studies are generally consistent with those of the WHI clinical trial.

After a mean follow-up of 5.6 years, the WHI trial reported an increased risk of breast cancer in women who took oestrogen plus progestogen. Observational studies have also reported an increased risk for oestrogen/progestogen combination therapy, and a smaller increased risk for oestrogen alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with oestrogen/progestogen combination therapy as compared to oestrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different oestrogens or among different oestrogen/progestogen combinations, doses, or routes of administration.

In the WHI trial of oestrogen plus progestogen, 26% of the women reported prior use of oestrogen alone and/or oestrogen/progestogen combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs 33 cases per 10,000 women-years, for oestrogen plus progestogen compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs 25 cases per 10,000 women-years, for oestrogen plus progestogen compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs 36 cases per 10,000 women-years for oestrogen plus progestogen compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the oestrogen plus progestogen group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of oestrogens alone or oestrogens plus progestogens compared to never users, while the oestrogen plus progestogen sub-study of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years.

The use of oestrogen plus progestogen has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

c. Liver tumour
In rare cases benign and in even rarer cases malignant liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage have been observed after the use of hormonal substances such as the one contained in PROGYNOVA. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential-diagnostic considerations.

3. Dementia

In the oestrogen alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomised women aged 65 to 79 years was randomised to 0.625 mg conjugated oestrogens or placebo. In the oestrogen plus progestogen WHIMS substudy, a population of 4,532 postmenopausal women aged 65 to 79 years was randomised to 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate or placebo.
In the oestrogen alone substudy, after an average follow-up of 5.2 years, 28 women in the oestrogen alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for 0.625 mg conjugated oestrogens alone versus placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for 0.625 mg conjugated oestrogens alone versus placebo was 37 versus 25 cases per 10,000 women-years.

In the oestrogen plus progestogen substudy, after an average follow-up of 4 years, 40 women in the oestrogen plus progestogen group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for oestrogen plus progestogen versus placebo was 2.05 (95% CI 1.21-3.48). The absolute risk of probable dementia for 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate versus placebo was 45 versus 22 cases per 10,000 women-years.

Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women (see BOXED WARNING and PRECAUTIONS, Use in the Elderly).

4. Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving oestrogens has been reported.

5. Hypercalcemia

Oestrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving oestrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilloedema or retinal vascular lesions, oestrogens should be discontinued.

7. General Precautions

a. Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to oestrogens. In a large, randomised, placebo-controlled clinical trial, a generalised effect of oestrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals during oestrogen use.

b. Hypertriglyceridemia
In patients with pre-existing hypertriglyceridemia, oestrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

c. Impaired liver function and past history of cholestatic jaundice
Oestrogens may be poorly metabolised in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past oestrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

d. Hypothyroidism
Oestrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving oestrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

e. Fluid retention
Because oestrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when oestrogens are prescribed.

f. Hypocalcemia
Oestrogens should be used with caution in individuals with severe hypocalcemia.

g. 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 oestrogen-only and combined 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). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

These associations were not shown in 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).

h. Exacerbation of endometriosis
Endometriosis may be exacerbated with administration of oestrogen therapy.

i. Exacerbation of other conditions
Oestrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in patients with these conditions.

j. Other conditions and product specific precautions
Treatment should be stopped at once if migrainous or frequent unusually severe headaches occur for the first time, or if there are other symptoms that are possible premonitory signs of cerebrovascular occlusion.

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

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

Should there be a suspicion of a prolactinoma, this should be ruled out before starting treatment.

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: benign breast disease, otosclerosis and chorea minor.

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

Carcinogenicity and Mutagenicity

Carcinogenic potential

Supra-physiological doses of 17β-oestradiol have been associated with the induction of tumours in oestrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established.

Mutagenic potential

There is limited evidence available in the literature suggesting that 17β-oestradiol may be weakly genotoxic at high doses. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy in mammalian cells, and two groups reported an increase incidence of sister chromatid exchanges, indicative of DNA damage. Neither of these latter effects were induced by 17β-oestradiol in human lymphocyte cultures. Importantly, there was no evidence of micronuclei formation in well controlled rodent bone marrow assays.

Use in Pregnancy (Category B3)

PROGYNOVA is contraindicated during pregnancy (see CONTRAINDICATIONS). If pregnancy occurs during medication with PROGYNOVA, treatment must be discontinued immediately.

In animal studies, maternal administration of high doses of synthetic oestrogens produced urogenital malformations in the offspring. However, the relevance of the animal findings for the clinical use of 17β-oestradiol is uncertain.

Use in Lactation

PROGYNOVA is contraindicated during lactation (see CONTRAINDICATIONS).

Paediatric Use

PROGYNOVA is not indicated for use in children and adolescents.

Use in the Elderly

Of the total number of subjects in the oestrogen alone substudy of the Women's Health Initiative (WHI) study, 46% (n=4,943) were 65 years and over, while 7.1% (n=767) were 75 years and over. There was a higher relative risk (conjugated oestrogens (CE) vs placebo) of stroke in women less than 75 years of age compared to women 75 years and over.

In the oestrogen alone substudy of the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomised to CE (0.625 mg) or placebo. In the oestrogen alone group, after an average follow-up of 5.2 years, the relative risk (CE versus placebo) of probable dementia was 1.49 (95% CI 0.83-2.66).

Of the total number of subjects in the oestrogen plus progestogen substudy of the Women's Health Initiative study, 44% (n=7,320) were 65 years and over, while 6.6% (n=1,095) were 75 years and over. There was a higher relative risk (CE/MPA vs placebo) of stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age.

In the oestrogen plus progestogen substudy of WHIMS, a population of 4,532 postmenopausal women, aged 65 to 79 years, was randomised to CE/MPA (0.625 mg/2.5 mg) or placebo. In the oestrogen plus progestogen group, after an average follow-up of 4 years, the relative risk (CE/MPA versus placebo) of probable dementia was 2.05 (95% CI 1.21-3.48).

Pooling the events in women receiving CE or CE/MPA in comparison to those in women on placebo, the overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women (see BOXED WARNING and PRECAUTIONS, Dementia).

With respect to efficacy in the approved indications, there have not been sufficient numbers of elderly patients involved in studies utilising oestrogens to determine whether those over 65 years of age differ from younger subjects in their response to oestrogens.

Patients with Hepatic Impairment

PROGYNOVA has not been studied in hepatic impaired patients. PROGYNOVA is contraindicated in women with severe hepatic disease.

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.

INTERACTIONS WITH OTHER MEDICINES

The Product Information of concomitant medicines should be consulted to identify potential interactions.

Effects of Other Medicines on PROGYNOVA

Interactions can occur with medicines 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 (*hypericum perforatum*).

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 four 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, ketoconazole, itraconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the oestrogen.

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

Effect of PROGYNOVA on Other Medicines

In individual cases, the requirement for oral antidiabetics or insulin can change as a result of the effect on glucose tolerance.

Interaction with Alcohol

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

ADVERSE EFFECTS

In addition to the adverse effects listed in the CONTRAINDICATIONS and PRECAUTIONS, 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 or weight decrease

- Psychiatric disorders

Depressed mood, anxiety, libido decreased or 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

Oedema, fatigue

- Malignancy

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 PRECAUTIONS).

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

The most serious adverse reactions associated with the use of PROGYNOVA are described under PRECAUTIONS.

DOSAGE AND ADMINISTRATION

Hormone therapy should only be continued as long as the benefit in alleviation of severe symptoms outweighs the risk.

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 and PRECAUTIONS and should be repeated periodically. The frequency and nature of these examinations should be based on established practice guidelines, 6 monthly reviews are generally considered appropriate, and be adapted to the individual woman, but should generally include pelvic organs, including routine cervical cytology, abdomen, breasts and blood pressure. The need for continued therapy should be reconsidered at each review.

Unless otherwise prescribed by the doctor, 1 PROGYNOVA tablet is taken daily (either one beige 1 mg tablet or one blue 2 mg tablet) and the tablets are to be swallowed whole with some liquid. Each pack covers 28 days and treatment is continuous, which means that the next pack follows immediately without a break. 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.

Treatment may be started at any time provided that pregnancy has been excluded.

High-dosed and long-term use of unopposed oestrogens during the climacteric may increase the incidence of endometrial carcinoma. Endometrial hyperplasia should be avoided in unopposed oestrogen treatment. It is therefore mandatory to add a progestogen for the last 10-14 days of each month of therapy.

As a general rule, PROGYNOVA treatment should be discontinued every 6 months in order to verify the persistence of complaints requiring treatment. It is essential to adhere to the dosage scheme prescribed by the doctor and to keep the appointments made for gynaecological check-ups.

OVERDOSAGE

Acute toxicity studies indicate that even in the case of inadvertent intake of a multiple of the therapeutic dose, no acute toxicity risk is to be expected. Overdose may cause nausea and vomiting and withdrawal bleeding may occur in some women. Management of acute overdose should be supportive.

PRESENTATION AND STORAGE CONDITIONS

PROGYNOVA 1 mg: Blister strips with 28 yellow coloured tablets, each tablets containing 1 mg oestradiol valerate. Packs contain 2 blister strips. Store below 30°C.

PROGYNOVA 2 mg: Blister strips with 28 blue coloured tablets, each tablet containing 2 mg oestradiol valerate. Packs contain 2 blister strips. Store below 25°C.

Store all medicines according to the storage conditions listed on the pack and keep them out of reach of children. Do not take the tablets after the expiry date listed on the pack.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

19 August 1991

DATE OF MOST RECENT AMENDMENT

20 October 2016

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