

PRODUCT INFORMATION

PREMIA® Low Continuous

Conjugated Oestrogens USP and Medroxyprogesterone Acetate USP tablets.

NAME OF THE MEDICINE

PREMIA LOW 0.3/1.5 Continuous

Conjugated oestrogens 0.3 mg and medroxyprogesterone acetate 1.5 mg tablets.

PREMIA LOW 0.45/1.5 Continuous

Conjugated oestrogens 0.45 mg and medroxyprogesterone acetate 1.5 mg tablets.

DESCRIPTION

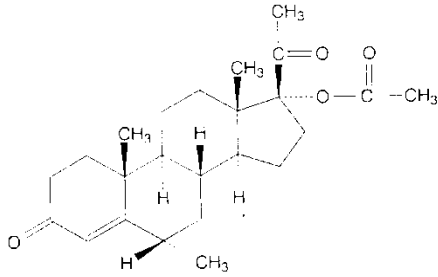
Each PREMIA LOW Continuous combined tablet has an inner PREMARIN® core and an outer coat containing micronised medroxyprogesterone acetate.

PREMIA LOW 0.3/1.5 Continuous cream coloured tablets contain the following excipients: calcium phosphate, anhydrous calcium sulfate, carnauba wax, microcrystalline cellulose, glyceryl mono-oleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze (shellac), macrogol 20000, povidone, sucrose, titanium dioxide, black ink and the colouring agent iron oxide yellow CI77492.

PREMIA LOW 0.45/1.5 Continuous gold coloured tablets contain the following excipients : calcium phosphate, anhydrous calcium sulphate carnauba wax, microcrystalline cellulose, glyceryl mono-oleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze (shellac), macrogol 2000, povidone, sucrose, titanium dioxide, black ink and the colouring agent iron oxide yellow CI77492.

Conjugated oestrogens are a mixture of natural oestrogens (equine origin) composed principally of the sodium salts of water-soluble sulfate esters of oestrone, equilin and 17 α -dihydroequilin, together with smaller amounts of 17 α -oestradiol, equilenin, 17 α -dihydroequilenin, 17 β -dihydroequilin, 17 β -dihydroequilenin, 17 β -oestradiol and δ 8, 9 dehydroestrone.

Medroxyprogesterone acetate (MPA) (6 α -methyl-3,20-dioxopregn-4-en-17 α -yl acetate) is a progestogen and a derivative of progesterone. It is a white to off-white, odourless, crystalline powder, stable in air, melting between 200 and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water. The structural formula is:



Molecular Formula C₂₄H₃₄O₄

M.W. 386.53

CAS No. [71-58-9]

PHARMACOLOGY

Pharmacodynamics

Oestrogen production occurs primarily in the ovarian follicles in women from the menarche to the menopause and is important in the development and maintenance of the female urogenital system and secondary sex characteristics.

During the menopause the ovarian-oestrogen production decreases and in postmenopausal women, when the ovaries have ceased to function, only a small amount of oestrogen is still produced.

This decrease and eventual cessation of oestrogen production in perimenopausal and postmenopausal women, respectively, may result in vasomotor symptoms (sweating, hot flushes) and atrophic vaginitis. In addition to relieving or eliminating these disorders, oestrogen replacement therapy has also been demonstrated to retard or halt the postmenopausal bone mass loss (osteoporosis).

The pharmacological effects of orally administered conjugated oestrogens are similar to those of endogenous oestrogens.

Medroxyprogesterone acetate induces responses in laboratory animals comparable to those caused by progesterone. Like progesterone, medroxyprogesterone acetate is thermogenic. It is more potent than progesterone. Medroxyprogesterone acetate induces glandular maturation in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses oestrous cycles. It is devoid of androgenic and oestrogenic activity. When administered cyclically or continuously in recommended doses to women with adequate oestrogen, it transforms proliferative into secretory endometrium. Medroxyprogesterone acetate may inhibit gonadotropin production, which in turn prevents follicular maturation and ovulation.

Pharmacokinetics

Conjugated oestrogens are soluble in water and are well absorbed from the gastrointestinal tract. Metabolism and inactivation occur primarily in the liver. Some oestrogens are excreted into the bile; however, they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water soluble oestrogen conjugates are strongly acidic and are ionised in body fluids, which favours excretion through the kidneys since tubular reabsorption is minimal.

Medroxyprogesterone acetate is an orally active progestational steroid and is rapidly absorbed after oral administration. There is high inter-individual variability in serum levels after administration of standard doses.

Medroxyprogesterone acetate is metabolised and conjugated in the liver. Metabolic products are predominantly excreted in the urine both as conjugated and free forms. Medroxyprogesterone acetate has an apparent half-life of about 30 hours.

Combined Therapy

PREMIA LOW combines conjugated oestrogens to replace oestrogen deficiency, with medroxyprogesterone acetate to prevent endometrial hyperstimulation.

Unopposed oestrogen treatment has been reported to increase the risk of endometrial carcinoma (see PRECAUTIONS: *Endometrial Cancer*). The addition of a progestogen such as medroxyprogesterone acetate to oestrogen replacement therapy, for at least 10-14 days of a cycle or on a continuous basis reduces the risk of the endometrium being hyperstimulated and therefore reduces the risk of any hyperplastic changes. Continuous oestrogen/progestogen therapy has been shown to be associated with the development of an atrophic endometrium and result in amenorrhoea in a majority of patients.

CLINICAL TRIALS

Women's Health Initiative Studies

The Women's Health Initiative (WHI), enrolled over 27,000 predominantly healthy postmenopausal women in two sub-studies to assess the major health benefits and risks of conjugated oestrogens (CE) [0.625 mg per day] alone or in combination with medroxyprogesterone acetate (MPA) [0.625 mg/2.5 mg per day] compared to placebo. The primary endpoint was the incidence of coronary heart disease (CHD), i.e. acute, nonfatal myocardial infarction (MI), silent MI and coronary death). The primary safety endpoint was incidence of invasive breast cancer. The study did not evaluate the effects of hormone replacement therapy (HT) on menopausal symptoms.

The WHI oestrogen plus progestogen (HT) sub-study was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events, at that time, exceeded the specified benefits (such as the reduction of colorectal cancer and hip fracture). Results of the HT sub-study of the WHI, which included 16,608 women (average age of 63 years; range 50 to 79) for an average follow-up of 5.6 years are presented in the table below.

In the WHI HT sub-study, an increase in CHD risk was associated with combined hormone therapy (Relative risk (RR) 1.24, 95% nominal confidence interval (nCI) 1.00-1.54). This was most apparent in the first year of the study (RR 1.81, 95% nCI 1.09-3.01). The RR of invasive breast cancer (RR 1.24, 95% nCI 1.01-1.54) was increased in women on combined hormone therapy. The sub-study also reported a statistically significant increased RR of overall stroke (RR 1.31, 95% nCI 1.02-1.68), ischaemic stroke (RR 1.44, 95% nCI 1.09-1.90), deep vein thrombosis (DVT) (RR 1.95, 95% nCI 1.43-2.67), and pulmonary embolism (PE) (RR 2.13, 95% nCI 1.45-3.11). Oestrogen plus progestogen was found to increase bone mineral density vs. placebo (3.7% vs. 0.14%, $P < 0.001$) after three years. A statistically significant reduced RR of hip (RR 0.67, 95% nCI 0.47-0.96),

vertebral (RR 0.65, 95% nCI 0.46-0.92), lower arm/wrist (RR 0.71, 95% nCI 0.59-0.85), and total fractures (RR 0.76, 95% nCI 0.69-0.83) was associated with oestrogen plus progestogen use.

Oestrogen plus progestogen use was associated with a statistically significant decreased risk of invasive colorectal cancer (RR 0.56, 95% nCI 0.38-0.81) although when colorectal cancers were diagnosed in combined hormone users, they were more advanced. Additional analyses showed no statistically significant differences in relative risk of endometrial (RR 0.81, 95% nCI 0.48-1.36) or cervical (RR 1.44, 95% nCI 0.47-4.42) cancers in patients on combined hormone replacement vs. placebo. After an average of 5.2 years of follow-up, the HT sub-study did not report a statistically significant effect on death due to other causes (RR 0.92, 95% nCI 0.74-1.14), and there was no effect on overall mortality risk (RR 0.98, 95% nCI 0.82-1.18). These confidence intervals are unadjusted for multiple looks and multiple comparisons.

RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN PLUS PROGESTOGEN SUBSTUDY OF WHI			
Event	Relative Risk HT vs. placebo at 5.6 Years (Nominal 95% CI*)	Placebo n = 8102	HT n = 8506
		Absolute Risk per 10,000 Person-years	
CHD events	1.24 (1.00-1.54)	33	39
Non-fatal MI	1.28 (1.00-2-1.63)	25	31
CHD death	1.10 (0.70-1.75)	8	8
All Strokes	1.31 (1.02-1.68)	24	31
Ischaemic Stroke	1.44 (1.09-1.90)	18	26
Deep vein thrombosis	1.95 (1.43-2.67)	13	26
Pulmonary embolism	2.13 (1.45-3.11)	8	18
Invasive breast cancer ^a	1.24 (1.01-1.54)	33	41
Invasive colorectal cancer	0.56 (0.38-0.81)	16	9
Endometrial cancer	0.81 (0.48-1.36)	7	6
Hip fracture	0.67 (0.47-0.96)	16	11
Vertebral fractures	0.65 (0.46-0.92)	17	11
Lower arm/wrist fractures	0.71 (0.59-0.85)	62	44
Total fractures	0.76 (0.69-0.83)	199	152
Death due to other causes ^{b,c}	0.92 (0.74-1.14)	40	37
Overall mortality ^c	0.98 (0.82-1.18)	53	52

^a Includes metastatic and non-metastatic breast cancer with the exception of *in situ* breast cancer.

^b All deaths, except for breast or colorectal cancer, definite/probable CHD, PE, or cerebrovascular disease.

^c Centrally adjudicated results not available for specified outcomes; results represent 5.2 years of data.

The oestrogen-alone (ET) sub-study 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 ET sub-study, which included 10,739 women (average age of 63 years, range 50 to 79) after an average follow-up of 6.8 years are presented in the table below.

In the ET sub-study of WHI there was no significant overall effect on the relative risk (RR) of CHD (RR 0.91, 95% nominal confidence interval [nCI] 0.75- 1.12); a slightly elevated RR of CHD was reported in the early follow-up period and diminished over time. There was no significant effect on the RR of invasive breast cancer (RR 0.77, 95% nCI 0.59-1.01) or colorectal cancer (RR 1.08, 95% nCI 0.75-1.55) reported. Oestrogen use was associated with a statistically significant increased risk of stroke (RR 1.39, 95% nCI 1.10-1.77) and DVT (RR 1.47, 95% nCI 1.04-2.08). The RR of PE (RR 1.34, 95% nCI 0.87-2.06) was not significantly increased. A statistically significant reduced risk of hip, vertebral and total fractures was reported with oestrogen use (RR 0.61, 95% nCI 0.41-0.91), (RR 0.62, 95% CI 0.42-0.93), and (RR 0.70, 95% nCI 0.63-0.79), respectively. The ET sub-study did not report a statistically significant effect on death due to other causes (RR 1.08, 95% nCI 0.88-1.32) or an effect on overall mortality risk (RR 1.04, 95% nCI 0.88-1.22). These confidence intervals are unadjusted for multiple looks and multiple comparisons. Only the reduced risk of total fractures remained statistically significant when based on adjusted confidence intervals.

RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN SUBSTUDY OF WHI ^a			
Event	Relative Risk ET vs. placebo At 6.8 Years (Nominal 95% CI [*])	Placebo n = 5429	ET n = 5310
		Absolute risk per 10,000 Person-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^b	0.77 (0.59-1.01)	33	26
Stroke^c	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^c	0.61 (0.41-0.91)	17	11
Death due to causes^d	1.08 (0.88-1.32)	50	53
Overall mortality	1.04 (0.88-1.22)	78	81
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;291:1701-12

^b Narrowly missed statistical significance (p = 0.06)

^c Statistically significant, p ≤ 0.05 *confidence intervals unadjusted for multiple looks and multiple comparisons.

^d All deaths, except from breast or colorectal cancer, definite/probable CHD, PE, or cerebrovascular disease.

* Confidence intervals unadjusted for multiple looks and multiple comparisons. Only the reduced risk of total fractures remained statistically significant when based on adjusted confidence intervals.

Women's Health Initiative Memory Study

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, one population of 4,532 women aged 65 to 79 years was randomised to conjugated oestrogens plus MPA (0.625 mg/2.5 mg) or placebo. In a second population of WHIMS 2,947 hysterectomised women, aged 65-79 years, were randomised to conjugated oestrogens (0.625 mg) or placebo. After an average follow-up of 4 years, a relative risk of 2.05 (95% CI 1.21-3.48) for probable dementia was observed in the oestrogen plus progestogen group compared to placebo. In the oestrogen-alone group, after an average follow-up of 5.2 years, a relative risk of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. The overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60) when data from the oestrogen-alone and the oestrogen plus

progestogen groups of WHIMS were combined. When the data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since this study was conducted in women aged 65-79 years, it is unknown whether these findings apply to younger postmenopausal women (see PRECAUTIONS: Dementia).

Clinical Studies – Vasomotor Symptoms

A double blind, randomised trial was conducted in a total of 1724 postmenopausal women for 13 cycles (28 days per cycle) to compare the safety and efficacy of the following conjugated oestrogens/medroxyprogesterone acetate (MPA) treatment regimens: Group A received 0.625 mg/2.5 mg continuously; Group B received 0.625 mg/5 mg continuously; Group C received 0.625 mg/5 mg cyclically and Group D received 0.625 mg/10 mg cyclically. The control group received PREMARIN 0.625 mg continuously.

Endometrial Effect

The clinical data indicates that MPA administered in the recommended dose to women with intact uteri receiving PREMARIN 0.625 mg reduces the incidence of hyperplastic changes and hence reduces the risk of developing adenocarcinoma. The addition of MPA did not adversely affect the ability of PREMARIN 0.625 mg to relieve menopausal symptoms. The following table summarises:

Incidence of endometrial hyperplasia after one year of treatment

	Premarin/MPA Continuous 0.625 mg/2.5 mg	Premarin/MPA Continuous 0.625 mg/5 mg	Premarin/MPA Cyclic 0.625 mg/5 mg	Premarin/MPA Cyclic 0.625 mg/10 mg	Premarin 0.625 mg Continuous
Total number of patients	279	274	277	272	283
Percent (No.) of patients with biopsies indicating hyperplasia	<1% (2)*	0*	1% (3)*	0*	20% (57)

*statistically significant ($p < 0.001$) in comparison to PREMARIN 0.625 mg alone

Breakthrough Bleeding

The results show that a significantly greater percentage of women taking the 5 mg regimen of PREMARIN/MPA Continuous have no bleeding or spotting after 6 cycles of therapy compared to the 2.5 mg regimen of PREMARIN/MPA Continuous.

Incidence of amenorrhoea for at least cycles 7 through 13. Percent (number of patients)

Population	PREMARIN/MPA Continuous 0.625 mg/2.5 mg	PREMARIN/MPA Continuous 0.625 mg/5 mg
Completed 13 cycles	40.4% (82/203)	52.6%* (101/192)

*significantly ($p < 0.05$) different in comparison to the 2.5 mg regimen of PREMARIN/MPA Continuous

INDICATIONS

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

The PREMIA LOW range is indicated:

As replacement therapy for oestrogen deficiency states associated with the climacteric in women with an intact uterus most commonly manifested by:

- a) Moderate to severe vasomotor symptoms associated with oestrogen deficiency in natural and surgical menopause (sweating, hot flushes).
- b) Atrophic Vaginitis.

When prescribing solely for the treatment of symptoms of vaginal atrophy, topical vaginal products should be considered.

There is no evidence that oestrogens are effective for anxiety or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.

For the prevention of postmenopausal osteoporosis.

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and future fracture, in whom non-oestrogen medications are not considered to be appropriate.

CONTRAINDICATIONS

Known or suspected pregnancy and lactation

Known, suspected or past cancer of the breast

Undiagnosed abnormal urogenital tract bleeding

Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis, pulmonary embolism)

Active or recent arterial thromboembolic disease (e.g. stroke, myocardial infarction)

Known thrombophilic disorders

Hypersensitivity to any ingredients contained in PREMIA LOW or PREMARIN

Liver dysfunction or disease as long as liver function tests have failed to return to normal

Severe uncontrolled hypertension

Other undiagnosed breast pathology

Known or suspected oestrogen dependent neoplasia (e.g. endometrial cancer, endometrial hyperplasia)

PRECAUTIONS

HT should not be initiated or continued to prevent or to treat cardiovascular disease or dementia (see PRECAUTIONS: Cardiovascular Disorders and Dementia).

The benefits and risks of HT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. In most circumstances, the risks of long-term HT outweigh the benefits. 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. In the absence of comparable data, the risks of HT should be assumed to be similar for all oestrogens and oestrogen/progestogen combinations.

HT has been associated with increased risks of certain cancers and cardiovascular disease.

Combined hormone replacement therapy should not be used for the long term maintenance of general health, including the primary or secondary prevention of cardiovascular disease. Oestrogen or oestrogenic compounds must not be used alone as hormone replacement therapy in women who have not had a hysterectomy.

Cardiovascular Disorders

HT has 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).

Patients who have risk factors for thrombotic disorders should be kept under careful observation.

Coronary Heart Disease and Stroke

In the oestrogen plus progestogen sub-study of the WHI (see CLINICAL TRIALS: Women's Health Initiative Studies) an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction, silent MI or death due to CHD) was observed in women receiving the oestrogen/progestogen combination (CE 0.625 mg plus MPA 2.5 mg) compared to women receiving placebo (41 vs. 34 per 10,000 person-years). The increase in risk was observed in year one and persisted.

In the same sub-study of WHI, an increased risk of stroke was observed in women receiving the oestrogen/progestogen combination compared to women receiving placebo (33 vs. 25 per 10,000 person-years). The increase in risk was observed after the first year and persisted. Should a stroke occur or be suspected, oestrogens should be discontinued immediately.

Patients who are at risk of developing migraines with aura may be at risk of ischemic stroke and should be kept under careful observation.*

In the oestrogen alone (ET) sub-study of WHI (see CLINICAL TRIALS: Women's Health Initiative Studies) no effect on CHD events was reported in women receiving oestrogen alone compared to placebo. A slightly elevated relative risk of CHD was reported in the early follow up period, and diminished over time on the oestrogen alone group.

In the same sub-study of WHI, an increased risk of stroke was observed in women receiving oestrogen alone compared to women receiving placebo (44 vs. 32 per 10,000 person-years). The increase in risk was observed during year one 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 Estrogen/progestin Replacement Study; HERS), treatment with oral conjugated oestrogens plus medroxyprogesterone acetate demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with oral conjugated oestrogens plus 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 hormone-treated group than in the placebo group in year 1, but not during the subsequent years.

Venous Thromboembolism

In the oestrogen plus progestogen sub-study of WHI (see CLINICAL TRIALS: Women's Health Initiative Studies) a 2-fold greater rate of VTE, (deep venous thrombosis and pulmonary embolism) was observed in women receiving the oestrogen/progestogen combination, compared to women receiving placebo. The absolute risk of VTE was 35 per 10,000 person-years in the oestrogen/progestogen combination group compared to 17 per 10,000 person-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

In the oestrogen-alone sub-study of WHI, the risk of VTE was reported to be increased for women taking conjugated oestrogens (28 vs. 21 per 10,000 person-years), although only the increased risk of DVT reached statistical significance (P=.03). The increase in VTE risk was observed during the first year. Recognised risk factors for VTE include, but are not limited to, a personal history or family history of VTE, obesity and systemic lupus erythematosus.

The physician should be aware of the possibility of thrombotic disorders (including thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism) during hormone replacement therapy and alert to their earliest manifestations. Should any of these occur or be suspected, hormone replacement therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

If feasible, PREMIA LOW should be discontinued at least four to six weeks before surgery of the type associated with increased risk of thromboembolism or during periods of prolonged immobilisation.

Malignant Neoplasms

Breast Cancer

In some studies use of ET and HT has been associated with an increased risk of breast cancer.

In the oestrogen plus progestogen sub-study of WHI, there was an increased risk of invasive breast cancer (RR 1.24, 95% nCI 1.01-1.54); invasive breast cancers were larger and diagnosed at a more advanced stage in the active therapy group compared to those in the placebo group. Metastatic disease was rare with no apparent difference between groups. Other prognostic factors such as histological subtype, grade and hormone receptor status did not differ between groups.

In the oestrogen-alone sub-study of WHI, after an average of 6.8 years of follow-up, conjugated oestrogens (0.625 mg per day) were not associated with an increased risk of breast cancer (RR 0.77, 95% CI 0.59-1.01).

Randomised and epidemiological studies (not necessarily including PREMIA LOW) have reported an increased risk of breast cancer in women taking oestrogens or oestrogen/progestogen combinations for HT for several years. The excess risk increases with duration of use and seems to return to normal in the course of about 5 years after stopping treatment. These studies also suggest that the risk of breast cancer is greater and becomes apparent earlier with oestrogen/progestogen combination therapy as compared to the use of oestrogens alone.

A separate cohort study (the Million Women Study) of women taking various hormone therapies suggested, with borderline significance, an increased relative risk of mortality due to breast cancers for current users compared to never users.

Studies evaluating various HT formulations did not show significant variation in the relative risk of breast cancer among formulations regardless of the oestrogen/progestogen components, doses, regimens, or route of administration.

According to epidemiological studies, about 32 women in every 1,000 women who have never used HT are expected to have breast cancer diagnosed between the ages of 50 and 65 years. Among 1,000 current or recent users of oestrogen-only preparations, it is estimated that 5 and 10 years of use beginning at age 50 result in 1.5 (95% confidence interval (CI), 0-3) and 5 (95% CI, 3-7), respectively, additional breast cancers diagnosed by age 65 years. The corresponding numbers for using oestrogen/progestogen combinations are 6 (95% CI, 5-7) and 19 (95% CI, 18-20).

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 health care provider and perform monthly breast self-examination. In addition, mammography examinations should be scheduled based on patient age, risk factors and prior mammogram results.

Endometrial Cancer

The use of unopposed oestrogens in women with an intact uterus has been associated with an increased risk of endometrial cancer.

The reported endometrial cancer risk among unopposed oestrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on oestrogen dose. Most studies show no significant increased risk associated with use of oestrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8-15 years after ERT is discontinued.

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 ERT has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer (see PRECAUTIONS: Addition of a Progestogen when a Woman has not had a Hysterectomy).

In a subset of WHI (see CLINICAL TRIALS: Women's Health Initiative Studies) no increased risk of endometrial cancer after an average of 5.2 years of treatment with the oestrogen/progestogen combination compared to placebo was observed.

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. Where no pathological cause is found, alteration in the dose or cycling may be indicated (see [DOSAGE AND ADMINISTRATION](#)).

NOTE: In perimenopausal patients where the endometrium is still proliferative, persistence of the endometrial proliferation may occur during administration of hormone replacement therapy. An endometrial biopsy may be performed at the discretion of the attending physician.

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 lower incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone.

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

Ovarian Cancer

In some epidemiological studies, the use of oestrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiological studies have not found these associations. The analysis of the WHI data suggested that oestrogen plus progestogen therapy may increase the risk of ovarian cancer.

Dementia

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, one population of 4532 women aged 65 to 79 years was randomised to conjugated oestrogens plus MPA (0.625 mg/2.5 mg) or placebo. In a second population of WHIMS 2947 hysterectomised women,

aged 65-79 years, were randomised to conjugated oestrogens (0.625 mg) or placebo. After an average follow-up of 4 years, a relative risk of 2.05 (95% CI 1.21-3.48) for probable dementia was observed in the oestrogen plus progestogen group compared to placebo. In the oestrogen-alone group, after an average follow-up of 5.2 years, a relative risk of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. When data from the two populations was pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since this study was conducted in women aged 65-79 years, it is unknown whether these findings apply to younger postmenopausal women (see PRECAUTIONS: Use in the Elderly).

Physical Examination

A complete medical and family history should be obtained prior to initiating or reinstating PREMIA LOW therapy and all prospective and current users of HT should be advised of the risks and benefits of oestrogens (see PRECAUTIONS). Pre-treatment and subsequent physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs including histological endometrial assessment and Papanicolaou Smear. Before starting treatment pregnancy should be excluded. The need for continued treatment with HT should be reviewed at least on an annual basis.

Uterine Bleeding

Certain patients may develop abnormal bleeding (see PRECAUTIONS: Endometrial Cancer).

Gallbladder Disease

Women receiving PREMIA LOW should be monitored for gall-bladder disease. A 2- to 4-fold increase in the risk of gall-bladder disease requiring surgery in women receiving ET/HT has been reported.

Fluid Retention

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

Exacerbation of Other Conditions

ET/HT may cause an exacerbation of asthma, epilepsy, migraine with or without aura*, diabetes mellitus with or without vascular involvement, porphyria, otosclerosis, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

Endometriosis may be exacerbated with administration of ET/HT.

Impaired Liver Function

Oestrogens/progestogens may be poorly metabolised in patients with impaired liver function (See CONTRAINDICATIONS)

Jaundice

If jaundice develops in any patient receiving PREMIA LOW, the medication should be discontinued while the cause is investigated.

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, PREMIA LOW should be discontinued.

Angioedema

Exogenous oestrogens may induce or exacerbate symptoms of angioedema, particularly in patients with hereditary angioedema.

Elevated Blood Pressure

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

Hypertriglyceridaemia

Caution should be exercised in patients with pre-existing hypertriglyceridaemia since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this population. Women with pre-existing hypertriglyceridaemia should be followed closely during ET/HT.

Hypercalcaemia

PREMIA LOW should be used with caution in patients with metabolic bone diseases that are associated with hypercalcaemia or in patients with renal insufficiency.

Hypocalcaemia

Oestrogens should be used with caution in individuals with severe hypocalcaemia, and diseases that can predispose to severe hypocalcaemia.

Hypothyroidism

Patients dependent on thyroid hormone replacement therapy may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range (see PRECAUTIONS: Effects on Laboratory Tests).

Visual Abnormalities

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

Other

Patients who have a history of mental depression should be carefully observed. PREMIA LOW should be discontinued if the depression recurs to a serious degree.

PREMIA LOW is not an oral contraceptive, nor will it restore fertility. Patients should be advised that the resumption of vaginal bleeding associated with ET in postmenopausal women is not indicative of fertility. If administered to a woman of child bearing potential she should be advised to use non-hormonal methods of contraception.

Doses of PREMIA LOW in HT should not exceed the recommended dose.

Paediatric Use

Paediatric use is not indicated.

Use in the Elderly

Of the total number of subjects in the HT subset of WHI, 44% (n=7,320) were 65 years and over, while 6.6% (n=1,095) were 75 and over (see CLINICAL TRIALS). No significant differences in relative risks were observed between subjects 65 years and over compared to younger subjects. There was a higher relative risk of non-fatal stroke and invasive breast cancer in women 75 years and over compared to younger subjects. In women greater than 75 years, the increased risk of non-fatal stroke and invasive breast cancer observed in the HT group compared to the placebo group was 75 vs. 24 per 10,000 person-years and 52 vs. 12 per 10,000 person-years, respectively.

Of the total number of subjects in the oestrogen-alone sub-study of the 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 (CE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over.

In WHIMS, 2947 hysterectomised women, aged 65-79 years, were randomised to conjugated oestrogens (0.625 mg) or placebo; 81% (n=2383) were 65 to 74 while 19% (n=564) were 75 and over. Approximately 50% of the women had no prior ET use. After an average follow-up of 5.2 years, the absolute risk of developing probable dementia with oestrogen-alone was 37 cases per 10,000 person-years compared to 25 cases per 10,000 person-years with placebo (RR 1.49, 95% CI 0.83-2.66) (see PRECAUTIONS: Dementia).

The second population of WHIMS, including 4,532 women 65 years of age and older, was followed for an average of 4 years, 82% were 65 to 74 (n=3,729) while 18% (n= 803) were 75 years and over. Most women (80%) had no prior HT use. After an average follow-up of 4 years, the absolute risk of developing probable dementia with HT was 45 cases per 10,000 person-years compared to 21

cases per 10,000 person-years with placebo (RR 2.05, 95% CI 1.21-3.48) (see PRECAUTIONS: Dementia).

Alzheimer's disease was the most common classification of probable dementia in both the treatment groups and the placebo groups. Women treated with conjugated oestrogens, plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Seventy nine percent of the cases of probable dementia occurred in the 56% of women that were older than 70 years for the ET group, and 90% of the cases of probable dementia occurred in the 54% of women that were older than 70 years (see PRECAUTIONS: Dementia).

When data from the two populations were pooled, the absolute risk of developing probable dementia with either ET or HT was 41 cases per 10,000 person-years compared to 23 cases per 10,000 person-years with placebo (RR 1.76, 95% CI 1.19-2.60).

There have not been sufficient numbers of geriatric women involved in clinical studies utilising CE and MPA to determine whether those over 65 years of age differ from younger subjects in response to PREMIA LOW.

Use in Pregnancy

Category D

PREMIA LOW should not be used during pregnancy.

Use in Lactation

Lactating mothers should not use PREMIA LOW.

Carcinogenicity/Mutagenicity

Studies suggest that combination HT increases the risk of breast cancer, ovarian cancer and endometrial cancer in women in a time dependant manner (see [PRECAUTIONS](#)).

Long-term, continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina and liver.

Long-term toxicology studies with medroxyprogesterone acetate in the dog and monkey (parenteral administration) and in the rat (dietary administration) have disclosed:

Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules as did some of the control animals. The nodules appearing in the control animals were intermittent in nature whereas the nodules in the drug treated animals were larger, more numerous, persistent, and in some high dose animals were malignant. In dogs, the appearance of mammary nodules with administration of medroxyprogesterone acetate is associated with increased concentrations of growth hormone, which stimulates the development of the nodules. The induction of mammary nodules by medroxyprogesterone acetate via growth hormone stimulation is a mechanism that is unique to dogs and that has no correspondence in humans.

Some monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in the monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. Upon histopathological examination, these nodules were determined to be hyperplastic. The relevance of these findings with respect to humans has not been established.

When medroxyprogesterone acetate was administered in the diet to rats for 2 years, there was an increased incidence of pancreatic islet cell adenoma and carcinoma associated with dosages of 1 mg/kg/day and above. These changes were considered to result from chronic stimulation of pancreatic beta-cells in response to hyperglycaemia that was induced by the cortisol-like activity of medroxyprogesterone acetate. Since rats are highly sensitive to hormonal changes, this mechanism is not considered to be relevant to the clinical use of medroxyprogesterone acetate. There is no evidence that the therapeutic use of medroxyprogesterone acetate produces pancreatic hyperplasia or neoplasia in humans.

Interactions with Other Medicines

Data from a drug-drug interaction study involving PREMARIN and medroxyprogesterone acetate indicate that the pharmacokinetic disposition of both medicines is not altered when the medicines are co-administered. Other clinical drug-drug interaction studies have not been conducted with PREMIA LOW.

In vitro and *in vivo* studies have shown that 17 β -oestradiol, one of the components of conjugated oestrogens, is metabolised partially by cytochrome P450 3A4 (CYP3A4). Therefore, strong CYP3A4 inducers such as phenobarbitone, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations of 17 β -oestradiol. This may lead to a decreased effect and/or changes in the uterine bleeding profile. CYP3A4 inhibitors such as cimetidine, erythromycin, cyclosporin, grapefruit juice and ketoconazole may increase plasma concentrations of 17 β -oestradiol and may result in side effects.

Hot flushes and vaginal bleeding have been reported in patients taking ET/HT and St John's Wort (*Hypericum perforatum*). St. John's Wort may induce hepatic microsomal enzymes, which theoretically may result in reduced efficacy of ET/HT.

Aminoglutethimide administered concomitantly with medroxyprogesterone acetate tablets may significantly depress the bioavailability of medroxyprogesterone acetate.

Effects on Laboratory Tests

Pathologists should be advised that a patient is receiving HT when relevant specimens are submitted.

Certain endocrine and liver function tests may be affected by administration of PREMIA LOW:

Accelerated prothrombin time, partial thromboplastin time and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex and beta-thromboglobulin; decreased levels of anti-factor Xa and

antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG) leading to increased circulating corticosteroid and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Impaired glucose tolerance.

The response to metyrapone may be reduced.

Increased plasma HDL and HDL₂ cholesterol sub-fraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

The results of these tests should not be regarded as reliable until PREMIA LOW use has been discontinued for 1-2 months. Test results, which were abnormal, should then be repeated.

Gonadotropin levels.

Plasma cortisol levels.

Increased plasma oestrogen and progestogen levels.

ADVERSE EFFECTS

The most serious adverse reactions associated with the use of any of the PREMIA LOW range of products are indicated under PRECAUTIONS. The following adverse reactions have been reported and are listed in the table below in CIOMS frequency categories:

Very Common:	≥10%		
Common:	≥1%	and	<10%
Uncommon:	≥0.1%	and	<1%
Rare:	≥0.01%	and	<0.1%
Very Rare:	<0.01%.		

System Organ Class Adverse Reaction

Immune System Disorders

Rare: Urticaria, angioedema, anaphylactic/ anaphylactoid reactions,

Reproductive System and Breast Disorders

Very Common:	Breast pain
Common:	Breakthrough bleeding/dysmenorrhoea, spotting, breast tenderness, enlargement, discharge
Uncommon:	Change in menstrual flow, change in cervical ectropion and secretion,
Rare:	Galactorrhoea, increased size of uterine leiomyomata
Very Rare:	Endometrial hyperplasia

Gastrointestinal Disorders

Uncommon:	Nausea, bloating, abdominal pain/cramps
Rare:	Vomiting, pancreatitis, ischaemic colitis

Hepato-biliary Disorders

Rare:	Gallbladder disease
Very Rare:	Cholelithiasis/cholestatic jaundice

Infections and Infestations

Common:	Vaginitis
Uncommon:	Vaginal candidiasis

Neoplasms Benign and Malignant (including Cysts and Polyps)

Rare:	Breast cancer, ovarian cancer, fibrocystic breast changes
Very Rare:	Endometrial cancer, enlargement of hepatic hemangiomas

Musculoskeletal, Connective Tissue and Bone Disorders

Common:	Arthralgias, leg cramps
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Psychiatric Disorders

Common:	Depression
Uncommon:	Changes in libido, mood disturbances, dementia
Rare:	Irritability

Skin and Subcutaneous Tissue Disorders

Uncommon:	Acne, alopecia, pruritus
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Rare: Chloasma/melasma, hirsutism, rash
Very Rare: Erythema multiforme, erythema nodosum

Cardiac Disorders

Rare: Myocardial infarction

Vascular Disorders

Uncommon: Venous thrombosis, pulmonary embolism

Rare: Superficial thrombophlebitis

Respiratory, Thoracic and Mediastinal Disorders

Rare: Exacerbation of asthma

General Disorders and Administration Site Conditions

Uncommon: Oedema

Metabolism and Nutrition Disorders

Rare: Glucose intolerance

Very Rare: Exacerbation of porphyria, hypocalcaemia

Eye Disorders

Uncommon: Intolerance to contact lenses

Very Rare: Retinal vascular thrombosis

Nervous System Disorders

Uncommon: Anxiety, insomnia, dizziness, headache (including migraine)

Rare: Exacerbation of epilepsy, stroke

Very Rare: Exacerbation of chorea

Investigations

Common: Changes in weight (increase or decrease), increased triglycerides

Very Rare: Increase in blood pressure

DOSAGE AND ADMINISTRATION

PREMIA LOW is indicated for a continuous hormone replacement therapy regimen.

For the treatment of menopausal symptoms, patients should be re-evaluated periodically to determine if treatment for symptoms is still necessary. The benefits and risks of HT must always be carefully weighed, including the emergence of risks as therapy continues.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated pharmacological therapy. Postmenopausal women require an adequate daily intake of elemental calcium. Therefore when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation may also be required to ensure adequate daily intake in postmenopausal women.

The recommended daily administration for both prevention of postmenopausal osteoporosis and treatment of moderate to severe vasomotor symptoms is as one cream tablet daily. Tablets should be taken whole; they should not be divided, crushed or dissolved in the mouth.

A patient should not commence taking tablets from more than one blister simultaneously; all tablets in one blister should be taken before commencing a new blister.

A starting dose of 5 mg medroxyprogesterone acetate continuously is appropriate for those patients when cycles without bleeding are to be achieved. Consider lowering the dose to the 2.5 mg continuous regimen after achieving amenorrhoea or within 12 months of initiating therapy. If bleeding occurs following the reduction of medroxyprogesterone acetate to 2.5 mg consider resuming the 5 mg continuous regimen.

With PREMIA LOW therapy several bleeding patterns may occur. These may range from absence of bleeding to irregular bleeding. If bleeding occurs, it is frequently light spotting or moderate bleeding. Clinical studies have demonstrated that the incidence and severity of this bleeding may decrease with continued therapy (see CLINICAL TRIALS). Where bleeding is excessive and/or persistent, in the absence of any underlying pathology, a dosage adjustment of medroxyprogesterone acetate may be indicated (see DOSAGE AND ADMINISTRATION: Dosage Adjustment).

In the situation where sensitive patients experience any drug related side effects, the dosage of either or both medroxyprogesterone acetate or conjugated oestrogens may need to be modified (see DOSAGE AND ADMINISTRATION: [Dosage Adjustment](#)).

PREMIA LOW is indicated in women with a uterus to reduce the risk of endometrial hyperplasia and endometrial cancer associated with oestrogen replacement therapy. PREMARIN therapy alone is appropriate for hysterectomised patients.

The blister strip(s) are clearly marked to ensure that the patient takes the correct tablet each day of their cycle. For details of calendar pack configuration see [PRESENTATION](#).

Dosage Adjustment

Conjugated oestrogens: Patients who suffer from headaches, weight gain, bloating, mastalgia, (or heavy withdrawal bleeds with cyclic therapy), may require a temporary reduction of the conjugated oestrogens dose from 0.625 mg to 0.3 mg daily. Patients who experience a continuation of the oestrogen deficiency symptoms may require an increase in the dose of conjugated oestrogens but should not exceed 1.25 mg daily.

Medroxyprogesterone acetate: Where a patient experiences, for example, pre-menstrual syndrome-like symptoms, the dosage of medroxyprogesterone acetate may need to be reduced. Patients who experience bleeding during progestogen therapy may require an increase of the medroxyprogesterone acetate dose. The lowest practical dose of progestogen will not be the same for all women. Clinical studies have shown that at least 10 days of a progestogen administration is required to provide adequate endometrial protection against oestrogen-induced hyperstimulation. When using a daily dose of conjugated oestrogens 0.625mg, the minimum dose of medroxyprogesterone acetate required to provide endometrial protection is 5 mg for at least 10-14 days of a cycle or 2.5 mg for 28 days on a continuous basis.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oestrogen/progestogen-containing products by young children. Symptoms reported in association with overdosage include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue and headache. Withdrawal/breakthrough bleeding may occur in women. There is no specific antidote and further treatment, if necessary, should be symptomatic.

PRESENTATION AND STORAGE CONDITIONS

PREMIA LOW 0.3/1.5 Continuous tablets 4-week therapy pack (cream-coloured, marked with a W above 0.3/1.5): 1 x 28 tablets.

PREMIA LOW 0.45/1.5 Continuous tablets 4-week therapy pack (gold-coloured, marked with a W above 0.45/1.5): 1 x 28 tablets.

Store below 25°C.

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* Please note changes to the Data Sheet