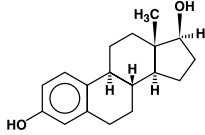


Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

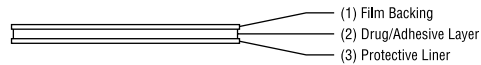
DESCRIPTION

Menostar® (estradiol transdermal system), is designed to provide nominal *in vivo* delivery of 14 mcg 17β-estradiol per day continuously upon application to intact skin. The period of use is 7 days. The transdermal system has a contact surface area of 3.25 cm², and contains 1 mg of estradiol USP.

Estradiol USP (17β-estradiol) is a white, crystalline powder, chemically described as *estra-1,3,5(10)-triene-3, 17β-diol*. It has an empirical formula of C₁₈H₂₄O₂ and molecular weight of 272.39. The structural formula is:



The Menostar transdermal system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film, and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the transdermal system can be used.



The active component of the transdermal system is 17β-estradiol. The remaining components of the transdermal system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

The Menostar transdermal system provides systemic estrogen therapy by releasing 17β-estradiol, the major estrogenic hormone secreted by the human ovary. Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estril, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

The decline of ovarian estrogen production that accompanies menopause or oophorectomy results in the acceleration of bone loss and bone resorption. Bone resorption is increased more than bone formation especially in the early years of menopause where bone loss is the greatest. In some women, these changes will eventually lead to decreased bone mass, osteoporosis and increased risk for fractures, particularly that of the spine, hip, and wrist. Vertebral fractures are the most common type of osteoporotic fracture in postmenopausal women.

Postmenopausal women with low serum estradiol concentrations and high serum concentrations of sex hormone-binding globulin (SHBG) have an increased risk of hip and vertebral fractures. Postmenopausal estrogen therapy decreases bone resorption, helping to reestablish balance between resorption and formation. This effect appears to be effective for as long as treatment is continued.

Pharmacokinetics

The bioavailability of estradiol following application of a Menostar transdermal system, relative to that of a transdermal system delivering 25 mcg/day, was investigated in 18 healthy postmenopausal women mean age 66 years (range 60-80 years). The mean serum estradiol concentrations upon administration of the two patches to the lower abdomen are shown in Figure 1. Transdermal administration of Menostar produced geometric mean serum concentration (C_{avg}) of estradiol of 13.7 pg/mL. No patches failed to adhere during the one week application period of both transdermal systems. Following application of the Menostar transdermal system to the abdomen, it is estimated to provide an average nominal *in-vivo* daily delivery of 14 mcg estradiol/day.

A. Absorption

The Menostar transdermal delivery system continuously releases estradiol which is transported across intact skin leading to sustained circulating levels of estradiol during a 7-day treatment period. The systemic availability of estradiol after transdermal administration is about 20 times higher than that after oral administration. This difference is due to the absence of first pass metabolism when estradiol is given by the transdermal route.

Figure 1
Mean Uncorrected Serum 17β-Estradiol Concentrations vs. Time Profile Following Application of Menostar and Climara® 6.5 cm² Transdermal System

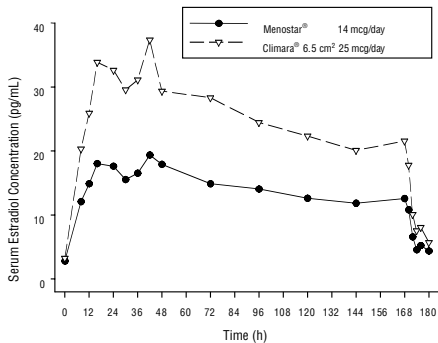


Table 1 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of Menostar using baseline uncorrected serum concentrations.

Table 1. Summary of Estradiol Pharmacokinetic Parameters (Abdomen Application)						
Product	Estradiol Daily Delivery Rate, mcg/day	AUC (0-tlast) pg·h/mL	C _{max} pg/mL	C _{avg} pg/mL	T _{max} h	C _{min} pg/mL
Menostar	14	2296	20.6	13.7	42	12.6
Climara® 6.5 cm ²	25	4151	37.2	24.7	42	20.4

Pharmacokinetic parameters are expressed in geometric means except for the t_{max} which represents the median estimate and the C_{min} which is expressed as the arithmetic mean.

The estimated estradiol daily delivery rate for Climara 6.5 cm² is quoted from the Climara labeling.

B. Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. In the clinical study with 208 patients on Menostar, SHBG concentration (mean ± SD) remained essentially unchanged over the 2 year period (baseline 45.1 ± 20.1 nmol/L, 24 month visit 46.4 ± 20.9 nmol/L).

C. Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estril, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

D. Excretion

Estradiol, estrone, and estril are excreted in the urine along with glucuronide and sulfate conjugates.

E. Special Populations:

Geriatric: The efficacy and safety of Menostar has been studied in women between 60 and 80 years of age, with approximately half over 65 years old.

Pediatric: No pharmacokinetic study for Menostar has been conducted in a pediatric population.

Gender: Menostar is indicated for use in postmenopausal women only.

Race: No studies were done to determine the effect of race on the pharmacokinetics of Menostar.

Patients with Renal Impairment: Total estradiol serum levels are higher in postmenopausal women with end stage renal disease (ESRD) receiving maintenance hemodialysis than in normal subjects at baseline and following oral doses of estradiol. Therefore, conventional transdermal estradiol doses used in individuals with normal renal function may be excessive for postmenopausal women with ESRD receiving maintenance hemodialysis.

Patients with Hepatic Impairment: Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

F. Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and ritampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

G. Adhesion

In a Menostar pharmacokinetic study with 18 postmenopausal women, no patches failed to adhere during the one week application period.

CLINICAL STUDIES

The efficacy of Menostar in the prevention of postmenopausal osteoporosis was investigated in a 2-year double blind, placebo-controlled, multicenter study in the United States. A total of 417 postmenopausal women, 60 to 80 years old, with an intact uterus were enrolled in the study. All patients received supplemental calcium and vitamin D.

Menostar produced larger increases in bone mass than placebo as reflected by dual-energy x-ray absorptiometric (DEXA) measurements of hip and lumbar spine BMD. The changes in BMD from baseline were statistically significantly ($p < 0.001$) greater during treatment with Menostar than during treatment with placebo for hip and spine after 1 and 2 years.

At lumbar spine Menostar increased BMD by 2.3% after 1 year and 3% after 2 years compared with a 0.5% increase after 1 and 2 years of treatment with placebo. At the hip Menostar increased BMD by 0.9% after one year and 0.84% after two years compared with a mean decrease of 0.22% after 1 year and 0.71% after 2 years of placebo treatment (see Table 2 below).

Time points	Lumbar spine			Total hip		
	Menostar N = 208	Placebo N = 209	p-value	Menostar N = 208	Placebo N = 209	p-value
12-month Endpoint	n = 189	n = 186	+2.29 +0.51 < 0.001	n = 189	n = 184	+0.9 -0.22 < 0.001
24-month Endpoint	n = 189	n = 186	+2.99 +0.54 < 0.001	n = 189	n = 185	+0.84 -0.71 < 0.001

N = total number of patients; n = number of patients with data available for each variable

The BMD data of the study were analyzed according to baseline estradiol levels of the patients. Overall, estimated treatment effects on lumbar spine and total hip BMD after 2 years were approximately twice as large in the subgroup with baseline estradiol levels < 5 pg/mL than in the subgroup with baseline estradiol levels ≥ 5 pg/mL [Table 3].

Baseline estradiol levels	Lumbar spine			Total hip		
	Menostar	Placebo	Treatment difference	Menostar	Placebo	Treatment difference
< 5 pg/mL	n = 101	n = 97	+3.5 +0.29 (p < 0.001)	n = 101	n = 96	+1.04 -1.09 (p < 0.001)
≥ 5 pg/mL	n = 88	n = 89	+2.4 +0.81 (p = 0.002)	n = 88	n = 89	+0.61 -0.31 (p = 0.045)

n = number of patients with data available for each variable

Menostar therapy also resulted in consistent, statistically significant suppression of bone turnover, as reflected by changes in serum and urine markers of bone formation (osteocalcin and bone-specific alkaline phosphatase) and bone resorption (carboxyterminal telopeptide of type 1 collagen (ICTP) and the urinary deoxypyridinoline/creatinine ratio).

Women's Health Initiative Studies

The WHI-enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral conjugated estrogens (CE 0.625 mg) alone per day or the use of oral conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) per day compared to placebo in the prevention of certain chronic diseases. The primary end-point 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 estrogen-alone substudy was stopped early because an increased risk of stroke was observed. Results of the estrogen-alone substudy, which included 10,739 women (average age 63 years, range 50 to 79; 75.3 percent white, 15 percent black, 6.1 percent Hispanic), after an average follow-up of 6.8 years are presented in Table 4.

Event ^c	Relative Risk* CE vs Placebo at 6.8 Years (95% CI)	CE	Placebo
		n = 5310	n = 5429
CHD events	0.91 (0.75-1.12)	49	54
Non-fatal MI	0.89 (0.7-1.12)	37	41
CHD death	0.94 (0.65-1.36)	15	16
Invasive breast cancer	0.77 (0.59-1.01)	26	33
Stroke	1.39 (1.1-1.77)	44	32
Pulmonary embolism	1.34 (0.87-2.06)	13	10
Colorectal cancer	1.08 (0.75-1.55)	17	16
Hip fracture	0.61 (0.41-0.91)	11	17
Death due to causes other than the events above	1.08 (0.88-1.32)	53	50
Global Index ^b	1.01 (0.91-1.12)	192	190
Deep vein thrombosis ^c	1.47 (1.04-2.08)	21	15
Vertebral fractures ^c	0.62 (0.42-0.93)	11	17
Total fractures ^c	0.7 (0.63-0.79)	139	195

^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 risks per 10,000 women-years in the group treated with CE alone was 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 WARNINGS, WARNINGS, and PRECAUTIONS.**) The CE/MPA substudy was 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 CE/MPA 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 5 below:

Event ^c	Relative Risk CE/MPA vs placebo at 5.2 Years (95% CI*)	CE/MPA	Placebo
		n = 8506	n = 8102
CHD events	1.29 (1.02-1.63)	37	30
Non-fatal MI	1.32 (1.02-1.72)	30	23
CHD death	1.18 (0.7-1.97)	7	6
Invasive breast cancer ^b	1.26 (1-1.59)	38	30
Stroke	1.41 (1.07-1.85)	29	21
Pulmonary embolism	2.13 (1.39-3.25)	16	8
Colorectal cancer	0.63 (0.43-0.92)	10	16
Endometrial cancer	0.83 (0.47-1.47)	5	6
Hip fracture	0.66 (0.45-0.98)	10	15
Death due to causes other than the events above	0.92 (0.74-1.14)	37	40
Global Index ^c	1.15 (1.03-1.28)	170	151
Deep vein thrombosis ^d	2.07 (1.49-2.87)	26	13
Vertebral fractures ^d	0.66 (0.44-0.98)	9	15
Other osteoporotic fractures ^d	0.77 (0.69-0.86)	131	170

^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 "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 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 WARNINGS, WARNINGS, and PRECAUTIONS.**)

Women's Health Initiative Memory Study

The estrogen-alone WHIMS, a substudy of the WHI study, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45 percent were aged 65 to 69 years, 36 percent were 70 to 74 years and 19 percent were 75 years of age and older) to evaluate the effects of conjugated estrogens (CE 0.625 mg) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-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 estrogen-alone group was 1.49 (95 percent confidence interval (CI), 0.83-2.66) compared to placebo. It is unknown whether these findings apply to postmenopausal women. (See **Boxed WARNINGS, WARNINGS, Dementia, and PRECAUTIONS, Geriatric Use.**) The estrogen plus progestin WHIMS substudy of WHI enrolled 4,532 predominantly 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 CE/MPA (0.625 mg conjugated estrogens 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 estrogen/progestin 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 WARNINGS, WARNINGS, Dementia, and PRECAUTIONS, Geriatric Use.**)

INDICATIONS AND USAGE

Menostar is indicated for the prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be considered only for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

Risk factors for osteoporosis include low bone mineral density, low estrogen levels, family history of osteoporosis, previous fracture, small frame (low BMI),

light skin color, smoking, and alcohol intake. Response to therapy can be predicted by pre-treatment serum estradiol (see Table 3), and can be assessed during treatment by measuring biochemical markers of bone formation/resorption, and/or bone mineral density.

CONTRAINDICATIONS

Menostar should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding.
- Known, suspected, or history of cancer of the breast.
- Known or suspected estrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
- Active or recent (e.g. within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
- Liver dysfunction or disease.
- Menostar should not be used in patients with known hypersensitivity to its ingredients.
- Known or suspected pregnancy. There is no indication for Menostar in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (See **PRECAUTIONS.**)

WARNINGS

See **Boxed WARNINGS.**

1. Cardiovascular disorders.

Estrogen and estrogen/progestin 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, estrogens 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 WHI estrogen-alone substudy, an increased risk of stroke was observed in women receiving CE compared to placebo (44 versus 32 per 10,000 women-years). (See **CLINICAL STUDIES.**)

In the CE/MPA substudy of the WHI study, an increased risk of CHD events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 versus 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same substudy of the WHI study, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 versus 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted. (See **CLINICAL STUDIES.**)

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 CE/MPA (0.625 mg/2.5mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-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 CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE)

In the WHI estrogen-alone substudy, an increased risk of deep vein thrombosis was observed in women receiving CE compared to placebo (21 versus 15 per 10,000 women-years). The increase in deep vein thrombosis risk was observed during the first year. (See **CLINICAL STUDIES.**)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA 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. (See **CLINICAL STUDIES.**)

The use of estrogen plus progestin 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.

3. Dementia

In the estrogen-alone WHIMS, a population of 2,947 hysterectomized women 65 to 79 years was randomized to CE or placebo. In the estrogen plus progestin WHIMS, a population of 4,532 postmenopausal women 65 to 79 years was randomized to CE/MPA or placebo.

In the estrogen-alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for estrogen-alone versus placebo was 37 versus 25 cases per 10,000 women-years. It is unknown whether these findings apply to younger post-menopausal women. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use.**)

After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8 percent, n=2,229) and 21 women in the placebo group (0.9 percent, n=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95 percent CI, 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger post-menopausal women. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use.**) It is unknown whether these findings apply to estrogen alone therapy.

4. Gallbladder disease

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

5. Hypercalcemia

Estrogen 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 estrogens. 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 papilledema or retinal vascular lesions, estrogens should be discontinued.

PRECAUTIONS

A. General

1. Addition of a progestin when a woman has not had a hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a low-ered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

2. Elevated blood pressure

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

3. Hypertriglyceridema

In patients with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. Impaired liver function and past history of cholestatic jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. Hypothyroidism

Estrogen 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 T₄ and T₃ serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens 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.

6. Fluid retention

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

7. Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

8. Ovarian cancer

The CE/MPA sub-study of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiological studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

9. Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of estrogens. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

10. Exacerbation of other conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

B. Patient Information

Physicians are advised to discuss the Patient Information leaflet with patients for whom they prescribe Menostar.

C. Laboratory Tests

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g. estradiol, FSH).

D. Drug/Laboratory Test Interactions

- 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 antifactor 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) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- Increased plasma HDL and HDL₂ subfraction concentrations, reduced LDL cholesterol concentration, and in oral formulations increased triglyceride levels.

- Impaired glucose tolerance.
- Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS.**)

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

F. Pregnancy

Menostar should not be used during pregnancy. (See **CONTRAINDICATIONS.**)

G. Nursing Mothers

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Menostar is administered to a nursing woman.

H. Pediatric Use

The safety and efficacy of Menostar in pediatric patients has not been established.

I. Geriatric Use

A total of 417 postmenopausal women 61-79 years old, with an intact uterus, participated in the osteoporosis trial. More than 50% of women receiving study drug, were considered geriatric (65 years or older). Efficacy in older (>65 years) and younger (<65 years) postmenopausal women in the osteoporosis treatment trial was comparable both at 12 and 24 months. Safety in older (>65 years) and younger (<65 years) postmenopausal women in the osteoporosis treatment trial was also comparable throughout the study.

Of the total number of subjects in the estrogen-alone substudy of the WHI study, 46 percent (n = 4,943) were 65 years and older, while 7.1 percent (n = 767) were 75 years and older. There was a higher relative risk (CE versus placebo) of stroke in women less than 75 years of age compared to women 75 years and older.

In the estrogen-alone substudy of the WHIMS, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to estrogen-alone (CE 0.625 mg) or placebo. In the estrogen-alone group, after an average follow-up of 5.2 years, the relative risk (CE versus placebo) of probable dementia was 1.49 percent (95 percent CI, 0.83-2.66)

Of the total number of subjects in the estrogen plus progestin substudy of the WHI study, 44 percent (n = 7,320) were 65 years and older, while 6.6 percent (n = 1,095) were 75 years and older. There was a higher relative risk (CE/MPA versus placebo) of stroke and invasive breast cancer in women 75 and older compared to women less than 75 years of age.

In the estrogen plus progestin substudy of WHIMS, a population of 4,532 post-menopausal women, aged 65 to 70 years, was randomized to conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) or placebo. In the estrogen plus progestin group, after an average follow-up of 4 years, the relative risk (CE/MPA versus placebo) of probable dementia was 2.05 (95 percent 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 of probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both substudies were conducted in women 65 to 79 years, it is unknown whether these findings apply to younger post-menopausal women. (See **BOXED WARNINGS** and **WARNINGS, Dementia.**)

ADVERSE REACTIONS

See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS.**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Summary of Most Frequently Reported Treatment Emergent Adverse Experiences/Medical Events (>5%) By Treatment Groups		
AE per Body System	Menostar 14 mcg/day (N=208)	Placebo (N=209)
Body as a Whole	95 (46%)	100 (48%)
Abdominal Pain	17 (8%)	17 (8%)
Accidental Injury	29 (14%)	23 (11%)
Infection	11 (5%)	10 (5%)
Pain	26 (13%)	26 (12%)
Cardiovascular	20 (10%)	19 (9%)
Digestive System	52 (25%)	44 (21%)
Constipation	11 (5%)	6 (3%)
Dyspepsia	11 (5%)	9 (4%)
Metabolic and Nutritional Disorders	25 (12%)	22 (11%)
Musculoskeletal System	54 (26%)	51 (24%)
Arthralgia	24 (12%)	13 (6%)
Arthritis	11 (5%)	15 (7%)
Myalgia	10 (5%)	6 (3%)
Nervous System	30 (14%)	23 (11%)
Dizziness	11 (5%)	6 (3%)
Respiratory System	62 (30%)	67 (32%)
Bronchitis	12 (6%)	9 (4%)
Upper Respiratory Infection	33 (16%)	35 (17%)
Skin and Appendages	50 (24%)	54 (26%)
Application Site Reaction	18 (9%)	18 (9%)
Breast Pain	10 (5%)	8 (4%)
Urogenital System	66 (32%)	40 (19%)
Cervical Polyps	13 (6%)	4 (2%)
Leukorrhea	22 (11%)	3 (1%)

The following additional adverse reactions have been reported with estrogens and/or progestin therapy.

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

4. Gastrointestinal

Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas.

5. Skin

Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

6. Eyes

Retinal vascular thrombosis; intolerance to contact lenses.

7. Central nervous system

Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy; dementia.

8. Miscellaneous

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; anaphylactoid/anaphylactic reactions including urticaria and angioedema; hypocalcemia; exacerbation of asthma; increased triglycerides.

OVERDOSAGE

Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females. Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children.

DOSAGE AND ADMINISTRATION

Menostar should only be prescribed to postmenopausal women who are at significant risk of osteoporosis. Non-estrogen medications should be carefully considered. Risk factors for osteoporosis include low bone mineral density, low estrogen levels, family history of osteoporosis, previous fracture, small frame (low BMI), light skin color, smoking, and alcohol intake. Response to therapy can be predicted by pre-treatment serum estradiol (see Table 3), and can be assessed during treatment by measuring biochemical markers of bone formation/resorption, and/or bone mineral density.

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be used, to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

It is recommended that women who have a uterus and are treated with Menostar receive a progestin for 14 days every 6 to 12 months and undergo an endometrial biopsy at yearly intervals or as clinically indicated. (See **BOXED WARNINGS** and **WARNINGS**).

Application of the System

The adhesive side of the Menostar transdermal system should be placed on a clean, dry area of the lower abdomen. **Menostar should not be applied to or near the breasts.** The sites of application must be rotated, with an interval of at least 1-week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub and remove the transdermal system. Application to areas where sitting would dislodge the transdermal system should also be avoided. The transdermal system should be applied immediately after opening the pouch and removing the protective liner. The transdermal system should be pressed firmly in place with the fingers for about 10 seconds, making sure there is good contact, especially around the edges. If the transdermal system lifts, apply pressure to maintain adhesion. In the event that a transdermal system should fall off, a new transdermal system should be applied for the remainder of the 7-day dosing interval. Only one system should be worn at any one time during the 7-day dosing interval. Swimming, bathing, or using a sauna while using Menostar has not been studied, and these activities may decrease the adhesion of the transdermal system and the delivery of estradiol.

Removal of the Transdermal System:

Removal of the system should be done carefully and slowly to avoid irritation of the skin. Should any adhesive remain on the skin after removal of the system, allow the area to dry for 15 minutes. Then gently rubbing the area with an oil-based cream or lotion should remove the adhesive residue.

Used patches still contain some active hormones. Each patch should be carefully folded in half so that it sticks to itself before throwing it away.

HOW SUPPLIED

Menostar (estradiol transdermal system), 14 mcg/day — each 3.25 cm² system contains 1 mg of estradiol USP

Individual Carton of 4 systems NDC 50419-455-04

Do not store above 86°F (30°C). Do not store unpouched. Apply immediately upon removal from the protective pouch.

PHARMACEUTICALS

PHARMACEUTICAL INFORMATION

Updated December 2005

Menostar® (Men-ō-star)

(estradiol transdermal system)

Read this before you start using Menostar and read what you get each time you refill Menostar. There may be new information. This information does not take the place of talk to your health care provider about your medical condition or your treatment.

What is the most important information I should know about Menostar (an osteoporosis preventative containing an estrogen hormone)? <ul style="list-style-type: none">Estrogens increase the chances of getting cancer of the uterus. <p>Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your health care provider should check any unusual vaginal bleeding to find out the cause.</p> <ul style="list-style-type: none">Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes. <p>Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.</p> <ul style="list-style-type: none">Using estrogens with or without progestins may increase your risk of dementia. <p>You and your healthcare provider should talk regularly about whether you still need treatment with Menostar.</p>

What is Menostar?

Menostar is a medicine that contains an estrogen hormone.

What is Menostar used for?

Menostar is used after menopause to:

- reduce your chances of getting osteoporosis (thin weak bones).** Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. Very low doses of estrogen can help keep your bones from becoming weaker. You and your healthcare provider should talk regularly about whether you should continue with Menostar.

Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances of getting post-menopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

Who should not use Menostar?

Do not start using Menostar if you:

- have unusual vaginal bleeding**
- currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your health care provider about whether you should use Menostar.

- had a stroke or heart attack in the past year.**

- currently have or have had blood clots.**

- currently have or have had liver problems.**

- are allergic to Menostar or any of its ingredients.** See the end of this leaflet for a list of ingredients in Menostar. If you are allergic to other estrogen patches, you will likely be allergic to Menostar.

- think you may be pregnant**

Tell your health care provider:

- if you are breastfeeding.** The hormone in Menostar can pass into your milk.
- about all of your medical problems.** Your health care provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Do not use any estrogen pill, patch or injection with Menostar. Some medicines may affect how Menostar works. Menostar may also affect how your other medicines work.
- if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens.

How should I use Menostar?

- Menostar is a patch that you wear on your skin. The estrogen in the Menostar patch passes through your skin. You must change your Menostar patch every 7 days (once a week). See the end of this leaflet for complete instructions for using Menostar.

- Estrogens should be used at the lowest dose possible for your treatment, only as long as needed. You and your healthcare provider should talk regularly about whether you still need treatment with Menostar.

What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your health care provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus (“fibroids”)
- Vaginal yeast infection

These are not all the possible side effects of Menostar. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with Menostar?

- Talk with your healthcare provider regularly about whether you should continue using Menostar. If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. In general, the addition of a progestin is recommended for women with a uterus to reduce the chance of getting cancer of the uterus.

- See your healthcare provider right away if you get vaginal bleeding while using Menostar.

- Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.

- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Menostar.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Menostar for conditions for which it was not prescribed. Do not give Menostar to other people, even if they have the same symptoms you have. It may harm them.

Keep Menostar out of the reach of children.

This leaflet provides a summary of the most important information about Menostar. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Menostar that is written for health professionals. You can get more information by calling the toll free number (1-888-237-5394) or visit www.menostar-us.com.

What are the ingredients in Menostar?

The active ingredient of Menostar is estradiol. Menostar also contains acrylate copolymer adhesive, fatty acid esters, and polyethylene backing. Menostar does not contain latex.

Instructions for Use

How and where do I apply the Menostar patch?

- Talk to your healthcare provider or pharmacist if you have questions about applying the Menostar patch.