Guidance for Industry

Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommended Prescribing Information for Health Care Providers and Patient Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

If you have questions on the content of the draft document contact Margaret Kober at (301) 796-0934.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2005
Labeling

Revision 4

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Guidance for Industry[1]
Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommended Prescribing Information for Health Care Providers and Patient Labeling

I. INTRODUCTION

This guidance describes, in labeling format, recommended prescribing information for estrogen drug products that treat moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy for new drug applications (NDAs) and for supplemental new drug applications (SNDAs). It also provides labeling recommendations for the Patient Information leaflet. For other indications, such as prevention of postmenopausal osteoporosis, manufacturers should contact the appropriate review division in the Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER).[2]

For abbreviated new drug applications (ANDAs), differences between the prescribing information for the reference listed drug and the prescribing information for the product covered by the ANDA may exist. These differences may include the expiration date, formulation, bioavailability, pharmacokinetics, or omission of an indication or other aspects of prescribing information protected by patent or accorded exclusivity under section 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act.

A draft of this guidance was first issued in October 1998 (63 FR 55399) and revised in September 1999 (64 FR 52100). However, on September 10, 2002, the Agency withdrew the draft guidance (67 FR 57432) pending consideration of the results from the National Institutes of

[1] This guidance has been prepared by the Division of Reproductive and Urologic Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] Drugs for the prevention or treatment of postmenopausal osteoporosis are reviewed by the Division of Metabolism and Endocrinology Products, OND, CDER.

Health (NIH) Women's Health Initiative (WHI) trial.[3] A third draft of this guidance was issued on February 3, 2003 (68 FR 5300) incorporating the results of the NIH estrogen plus progestin clinical trial. The fourth draft of this guidance was issued on February 17, 2004 (69 FR 7492) incorporating the results of the NIH Women's Health Initiative Memory Study (WHIMS).[4] This revised draft of this guidance, incorporating the results of the NIH estrogen-alone clinical trials, is being made available for comment.[5,6]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[3] The results of the NIH Women's Health Initiative estrogen plus progestin clinical trial were reported in the *Journal of the American Medical Association*, 2002; 288:321-333.

[4] The results of the NIH Women's Health Initiative Memory Study estrogen plus progestin clinical trial were reported in the *Journal of the American Medical Association*, 2003; 289:2651-2662.

[5] The results of the NIH Women's Health Initiative estrogen-alone clinical trial were reported in the *Journal of the American Medical Association*, 2004; 291:1701-1712.

[6] The results of the NIH Women's Health Initiative Memory Study estrogen-alone clinical trial were reported in the *Journal of the American Medical Association*, 2004; 291:2947-2958.

II. LABELING FOR HEALTH CARE PROVIDERS

We recommend including the following prescribing information for health care providers:

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, *Endometrial cancer***.)

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **WARNINGS, Cardiovascular disorders** and **Dementia**.)

The Women's Health Initiative (WHI) study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with oral conjugated estrogens (CE 0.625 mg) alone per day, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders**.)

The WHI study reported increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders** and **Malignant neoplasms, *Breast cancer***.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI study, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with CE 0.625 mg alone and during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES**, **WARNINGS, Dementia**, and **PRECAUTIONS, Geriatric Use**.)

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

This should be supplied by the manufacturer.

CLINICAL PHARMACOLOGY

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 estriol, 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.

A. Absorption

This section should be specific for the product in question. If the product in question is an oral dosage form, we recommend including the following information:

1. The rate and extent of absorption (e.g., C_{max}, T_{max}, C_{avg}, AUC, fluctuation index, and parent/metabolite ratio) generated during the clinical pharmacology and biopharmaceutical studies.

2. Dose proportionality data for the proposed dosing range.

3. The effect of food on the bioavailability of the product in question.

4. Tables and figures, including baseline unadjusted levels of estradiol and metabolites. In the event that baseline adjusted levels are more appropriate, this fact should be clearly indicated.

If the product in question is a transdermal delivery system, we recommend including the following information:

1. The rate and extent of absorption (e.g., C_{max}, T_{max}, C_{avg}, AUC, fluctuation index, and parent/metabolite ratio) generated during the clinical pharmacology and biopharmaceutical studies.

2. Data for all the anatomical application sites that will be proposed in the prescribing information.

3. Dose proportionality data for the proposed dosing range.

4. Tables and figures, including baseline unadjusted levels of estradiol and metabolites. In the event that baseline adjusted levels are more appropriate, this fact should be clearly indicated.

5. The nominal mean in vivo delivery rate.

If the product in question is a topical dosage form for vaginal administration or administration to another site and the estrogen is systemically available, we recommend including the following information:

1. The rate and extent of absorption (e.g., C_{max}, T_{max}, C_{avg}, AUC, fluctuation index, and parent/metabolite ratio) generated during the clinical pharmacology and biopharmaceutical studies.

2. Data for all the anatomical application sites that will be proposed in the prescribing information (except for vaginally administered products).

3. Dose proportionality data for the proposed dosing range.

4. Tables and figures, including baseline unadjusted levels of estradiol and metabolites. In the event that baseline adjusted levels are more appropriate, this fact should be clearly indicated.

If the product in question is a topical dosage form or a dosage form to be administered vaginally and the estrogen is not systemically available, we recommend stating this clearly.

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.

We recommend that additional protein binding and pharmacokinetic information be specific for the product in question.

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 estriol, 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.

We recommend that additional metabolic and pharmacokinetic information be specific for the product in question.

D. Excretion

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

We recommend that additional pharmacokinetic information (e.g., apparent half-life(s) and clearance) be specific for the product in question.

E. Special Populations

This section should be specific for the product in question.

F. Drug Interactions

We recommend including the following information:

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 rifampin, 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 result in side effects.

This section should be specific for the product in question. If the product in question is a transdermal delivery system, we recommend adding the following section on adhesion:

G. Adhesion

Since the adhesion or lack of adhesion of transdermal systems to the skin is a critical factor directly related to drug delivery, therapeutic effect, and possibly to compliance, we recommend including in vivo adhesion information on the percentage of systems that lifted and/or were detached and replaced during the pharmacokinetic and clinical studies. Adhesion information should be specific for the transdermal product in question.

CLINICAL STUDIES

This section should be specific for the product in question and should include information concerning the appropriate endpoints to assess the effectiveness for the indication sought. A concise and objective description of the studies that provide primary support for effectiveness should include brief summaries of the following:

a. Study designs
b. Demographics of the intent-to-treat study populations
c. Study results

For the indication of treatment of moderate to severe vasomotor symptoms, we recommend including a table of results (number and severity of vasomotor symptoms combined in a single table or reported in separate tables) that provides the sample size, the mean number (standard deviation (SD)) or mean severity (SD) of hot flashes per day or per week at baseline and at weeks 4 and 12 for each treatment group, the mean change (SD) for number and severity from baseline at weeks 4 and 12 for each treatment group, and the P-value versus placebo for number and severity at weeks 4 and 12 for each treatment group.

For the indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy, a description of the study results should be included in the text.

We recommend reporting results from individual studies separately.

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 endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The 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 of 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 *(insert number)*.

Table *(insert number)* **RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI**[a]

Event[c]	Relative Risk* Premarin vs. Placebo at 6.8 Years (95% CI)	Placebo n = 5,429	Premarin n = 5,310
		Absolute Risk per 10,000 Women-Years	
CHD events	0.91 (0.75-1.12)	54	49
Nonfatal MI	*0.89 (0.70-1.12)*	*41*	*37*
CHD death	*0.94 (0.65-1.36)*	*16*	*15*
Invasive breast cancer	0.77 (0.59-1.01)	33	26
Stroke	1.39 (1.10-1.77)	32	44
Pulmonary embolism	1.34 (0.87-2.06)	10	13
Colorectal cancer	1.08 (0.75-1.55)	16	17
Hip fracture	0.61 (0.41-0.91)	17	11
Death due to causes other than the events above	1.08 (0.88-1.32)	50	53
Global index[b]	1.01 (0.91-1.12)	190	192
Deep vein thrombosis[c]	1.47 (1.04-2.08)	15	21
Vertebral fractures[c]	0.62 (0.42-0.93)	17	11
Total fractures[c]	0.70 (0.63-0.79)	195	139

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

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with Premarin 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 percent white, 6.5 percent black, 5.5 percent Hispanic), after an average follow-up of 5.2 years are presented in Table *(insert number)*.

Table *(insert number)* **RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI**[a]			
Event[c]	Relative Risk CE/MPA vs. placebo at 5.2 Years (95% CI*)	Placebo n = 8,102	CE/MPA n = 8,506
		Absolute Risk per 10,000 Women-Years	
CHD events	1.29 (1.02-1.63)	30	37
Nonfatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global index[c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis[d]	2.07 (1.49-2.87)	13	26
Vertebral fractures[d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures[d]	0.77 (0.69-0.86)	170	131

[a] Adapted from JAMA, 2002; 288:321-333
[b] Includes metastatic and nonmetastatic 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 the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED 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 younger postmenopausal women. (See **BOXED WARNINGS**, **WARNINGS**, **Dementia**, and **PRECAUTIONS**, **Geriatric Use**.)

The estrogen plus progestin WHIMS substudy enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were aged 65 to 69 years, 35 percent were 70 to 74 years, and 18 percent were 75 years of age and older) to evaluate the effects of conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) 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 percent CI, 1.21-3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNING**, **WARNINGS**, **Dementia**, and **PRECAUTIONS, Geriatric Use**.)

INDICATIONS AND USAGE

(Trade Name) is indicated in the:

Depending on the specific drug, dosage form, and clinical trials performed, the prescribing information can include appropriate indications from those listed here.

1. Treatment of moderate to severe vasomotor symptoms associated with menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

CONTRAINDICATIONS

(Trade Name) should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.

2. Known, suspected, or history of cancer of the breast.

3. Known or suspected estrogen-dependent neoplasia.

4. Active deep vein thrombosis, pulmonary embolism, or history of these conditions.

5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).

6. Liver dysfunction or disease.

7. Known hypersensitivity to the ingredients of (Trade Name).

8. Known or suspected pregnancy. There is no indication for (Trade Name) 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 therapies 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 (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). The increase in risk was observed in year 1 and persisted. (See **CLINICAL STUDIES**.)

In the CE/MPA substudy of the WHI study, an increased risk of CHD events (defined as nonfatal 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 1 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 (0.625mg/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. Participation in an open label extension of the original HERS trial (HERS II) was agreed to by 2,321 women. 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 risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism

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 the WHI study, a twofold 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**.)

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

2. Malignant neoplasms

a. Endometrial cancer

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

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin

to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the CE/MPA substudy of the WHI study (see **CLINICAL STUDIES**). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of the WHI study reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about 5 years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen-alone therapy.

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

The 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 health care 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 aged 65 to 79 years was randomized to CE or placebo. In the estrogen plus progestin WHIMS, a population of 4,532 postmenopausal women aged 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 postmenopausal 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 postmenopausal women. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

4. Gallbladder disease

A two- to fourfold 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 permanently 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 lowered 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 estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertriglyceridemia

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 T_4 and T_3 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 to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention

Estrogens may cause some degree of fluid retention. Because of this, patients who have 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 substudy of the WHI study 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 epidemiologic studies, the use of estrogen alone, in particular for 10 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. Information for Patients

Physicians are advised to discuss the Patient Information leaflet with patients for whom they prescribe (Trade Name).

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).

This section should be specific for the product in question.

D. Drug/laboratory Test Interactions

1. 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.

2. Increased TBG levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay), or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), 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).

4. Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of estrogen, with or without progestin, in women with or 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.

This section should be specific for the product in question.

F. Pregnancy

(Trade Name) 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 (Trade Name) is administered to a nursing woman.

H. Pediatric Use

Complete as appropriate in accordance with 21 CFR 201.57(f)(9).

I. Geriatric Use

Complete as appropriate in accordance with 21 CFR 201.57(f)(10).

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 (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 postmenopausal 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 aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS, Dementia**.)

ADVERSE REACTIONS

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

This section should be revised to state the following when including a table of all treatment emergent adverse events regardless of drug relationship reported as a frequency of greater than or equal to 5 percent with Trade Name.

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.

We recommend including the following:

The following additional adverse reactions have been reported with estrogen 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 that 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; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaplylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Depending on the specific drug and dosage form, the prescribing information can include appropriate dosage and administration from those listed here.

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). 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.

The manufacturer should supply specific dosage information for treatment of moderate to severe vasomotor symptoms and for treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause.

For products with multiple doses:

Patients should be started at the lowest dose.

We recommend that manufacturers whose clinical development program did not identify the lowest effective dose include:

The lowest effective dose of (Trade Name) has not been determined.

HOW SUPPLIED

The manufacturer should supply information on available dosage forms, potency, color, and packaging. The manufacturer should also provide a storage statement.

The manufacturer should include a statement such as "Keep out of reach of children" in both the instructions and the dispenser.

III. PATIENT INFORMATION

The recommended text for the Patient Information leaflet is as follows:

PATIENT INFORMATION

(Updated *insert full date*)

Trade Name
(*Insert chemical name*)

Read this Patient Information leaflet before you start taking (Trade Name) and read what you get each time you refill (Trade Name). There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT (TRADE NAME) (AN ESTROGEN HORMONE)?

- Estrogens increase the chance of getting cancer of the uterus.

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.

- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.

Using estrogens with or without progestins may increase your chance of getting heart attacks, strokes, breast cancer, and blood clots.

- Do not use estrogens with or without progestins to prevent dementia.

Using estrogens with or without progestins may increase your risk of dementia.

You and your health care provider should talk regularly about whether you still need treatment with (Trade Name).

What is (Trade Name)?

(Trade Name) is a medicine that contains estrogen hormones.

What is (Trade Name) used for?

We recommend including only approved indications.

(Trade Name) is used after menopause to:

- **Reduce moderate to severe hot flashes**

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your health care provider should talk regularly about whether you still need treatment with (Trade Name).

- **Treat moderate to severe dryness, itching, and burning in and around the vagina**

You and your health care provider should talk regularly about whether you still need treatment with (Trade Name) to control these problems. If you use (Trade Name) only to treat your dryness, itching, and burning in and around your vagina, talk with your health care provider about whether a topical vaginal product would be better for you.

Who should not take (Trade Name)?

Do not start taking (Trade Name) if you:

- **Have unusual vaginal bleeding**

- **Currently have or have had certain cancers**

Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your health care provider about whether you should take (Trade Name).

- **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 (Trade Name) or any of its ingredients**

See the end of this leaflet for a list of ingredients in (Trade Name).

- **Think you may be pregnant**

Tell your health care provider:

- **If you are breastfeeding**

The hormone in (Trade Name) 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; problems with your heart, liver, thyroid, or kidneys; or have high calcium levels in your blood.

- **About all the medicines you take**

This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how (Trade Name) works. (Trade Name) 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.

What are the ingredients in (Trade Name)?

We recommend providing a list of all active and nonactive ingredients.

How should I take (Trade Name)?

We recommend providing instructions on how to take (Trade Name). If (Trade Name) comes in several strengths, include #1.

1. Start at the lowest dose and talk to your health care provider about how well that dose is working for you.

2. Estrogens should be used at the lowest dose possible for your treatment only as long as needed. (Sponsors whose clinical development program did not identify the lowest effective dose are recommended to include: The lowest effective dose of (Trade Name) has not been determined. You and your health care provider should talk regularly (e.g., every 3 to 6 months) about the dose you are taking and whether you still need treatment with (Trade Name)).

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**

Some of the warning signs of serious side effects include:

- **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 (Trade Name). For more information, ask your health care provider or pharmacist.

What can I do to lower my chances of a serious side effect with (Trade Name)?

Talk with your health care provider regularly about whether you should continue taking (Trade Name). If you have a uterus, talk to your health care 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 health care provider right away if you get vaginal bleeding while taking (Trade Name). Have a breast exam and mammogram (breast X-ray) every year unless your health care provider tells you otherwise. 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 a higher chance of getting heart disease. Ask your health care provider for ways to lower your chance of getting heart disease.

Have an annual gynecologic exam

General information about safe and effective use of (Trade Name)

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

Keep (Trade Name) out of the reach of children

This leaflet provides a summary of the most important information about (Trade Name). If you would like more information, talk with your health care provider or pharmacist. You can ask for information about (Trade Name) that is written for health professionals. You can get more information by calling the toll-free number *(add number here)*.