

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-788

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Synthetic Conjugated Estrogens, A Vaginal Cream safely and effectively. See full prescribing information for Synthetic Conjugated Estrogens, A Vaginal Cream.

(synthetic conjugated estrogens, A) Vaginal Cream
Initial U.S. Approval: 1999

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA FOR ESTROGEN ALONE THERAPY

See full prescribing information for complete boxed warning.

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (5.2)
- The Women's Health Initiative Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA FOR ESTROGEN PLUS PROGESTIN THERAPY

See full prescribing information for complete boxed warning.

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
- The WHI estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction (5.2)
- The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)
- The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

INDICATIONS AND USAGE

Synthetic Conjugated Estrogens, A, Vaginal Cream is a mixture of estrogens indicated for:

- Treatment of Moderate to Severe Vaginal Dryness, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause (1.1)
- Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause (1.2)

DOSAGE AND ADMINISTRATION

One (1) gram intravaginally daily for one week followed by 1 gram intravaginally twice a week. (2.2)

DOSAGE FORMS AND STRENGTHS

- 30 gram tube of cream (3)
- Each gram of cream contains 0.625 mg synthetic conjugated estrogens, A (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.3)
- Known or suspected estrogen-dependent neoplasia (4, 5.3)
- Active deep vein thrombosis, pulmonary embolism, or history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke and myocardial infarction) or a history of these conditions (4, 5.2)
- Known liver dysfunction or disease (4, 5.10)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- Monitor thyroid function in women on thyroid hormone replacement (5.12, 5.19)

ADVERSE REACTIONS

Most common adverse reactions (≥ 3 percent) are: headache, vulvovaginal infection, upper respiratory tract infection and hot flush. (6.1, 14.1)

To report SUSPECTED ADVERSE REACTIONS, contact Duramed Pharmaceuticals at 1-800-227-7522 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism. (7)

USE IN SPECIFIC POPULATIONS

- Nursing Women: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (5.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling

Revised:11/2008

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FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA FOR ESTROGEN-ALONE THERAPY

ENDOMETRIAL CANCER

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see *Warnings and Precautions* (5.3)].

CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see *Warnings and Precautions* (5.2, 5.4), and *Clinical Studies* (14.2, 14.3)].

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) (0.625 mg), relative to placebo [see *Warnings and Precautions* (5.2) and *Clinical Studies* (14.2)].

The Women's Health Initiative Memory Study (WHIMS) estrogen-alone ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.5) and *Clinical Studies* (14.3)].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

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.

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA FOR ESTROGEN PLUS PROGESTIN THERAPY

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [see *Warnings and Precautions* (5.2, 5.4), and *Clinical Studies* (14.2, 14.3)].

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg), relative to placebo [see *Warnings and Precautions* (5.2), and *Clinical Studies* (14.2)].

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see *Warnings and Precautions* (5.3), and *Clinical Studies* (14.2)].

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily 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 *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.5) and *Clinical Studies* (14.3)].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA therapy and other combinations and dosage forms of estrogens and progestins.

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.

1. INDICATIONS AND USAGE

Synthetic Conjugated Estrogens, A Vaginal Cream is indicated for:

- 1.1 Treatment of Moderate to Severe Vaginal Dryness, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause.
- 1.2 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal atrophy, due to Menopause.

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer.

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin [see *Warnings and Precautions* (5.3, 5.15)].

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. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2.2. Recommended Dosing

Synthetic Conjugated Estrogens, A Vaginal Cream 1 gram is administered intravaginally daily for one week followed by 1 gram administered intravaginally twice weekly.

3. DOSAGE FORM AND STRENGTH

Synthetic Conjugated Estrogens, A Vaginal Cream contains synthetic conjugated estrogens, A 0.625 mg per gram in a nonliquifying cream base.

4. CONTRAINDICATIONS

Synthetic Conjugated Estrogens, A Vaginal Cream therapy should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active deep vein thrombosis, pulmonary embolism or history of these conditions
- Active arterial thromboembolic disease (for example, stroke and myocardial infarction) or a history of these conditions
- Known liver dysfunction or disease
- Known or suspected pregnancy

5. WARNINGS AND PRECAUTIONS

5.1 Risks from Systemic Absorption

Systemic absorption occurs with the use of Synthetic Conjugated Estrogens, A Vaginal Cream. The warnings, precautions, and adverse reactions associated with oral synthetic conjugated estrogens, A treatment should be taken into account.

5.2 Cardiovascular Disorders

An increased risk of stroke and deep vein thrombosis (DVT) has been reported with estrogen-alone therapy. An increased risk of pulmonary embolism, DVT, stroke, and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogens with or without progestins should be discontinued immediately.

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

Stroke

In the Women's Health Initiative (WHI) estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted [see *Clinical Studies* (14.2)]. Should a stroke occur or be suspected, estrogens

should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) versus those receiving placebo (18 versus 21 per 10,000 women-years).¹

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in all women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to placebo (33 versus 25 per 10,000 women-years) [see *Clinical Studies (14.2)*]. The increase in risk was demonstrated after the first year and persisted.¹

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal myocardial infarction [MI], silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo² [see *Clinical Studies (14.2)*].

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE 0.625 mg compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).¹

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events in women receiving daily CE (0.625mg) plus MPA (2.5mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).¹ An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 [see *Clinical Studies (14.2)*].

In postmenopausal women with documented heart disease (n = 2,763), average age 66.7 years), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus 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 plus MPA-treated group than in the placebo group in year 1, but not during subsequent years. Two thousand, three hundred and twenty-one (2,321) 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 (0.625mg) plus MPA (2.5mg) group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism (VTE)

In the WHI estrogen-alone substudy, the risk of VTE (DVT and pulmonary embolism [PE]), was increased for women receiving daily CE (0.625 mg) compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women years). The increase in VTE risk was demonstrated during the first 2 years³ [see *Clinical Studies (14.2)*]. Should a VTE occur or be suspected, estrogens should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625mg) plus MPA (2.5mg) compared to women receiving placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and PE (18 vs. 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted⁴ [See *Clinical Studies (14.2)*]. Should a VTE occur or be suspected, estrogens should be discontinued immediately.

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.

5.3 Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, 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 to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital 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 in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the Women's Health Initiative (WHI) substudy of daily CE (0.625mg). In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg) was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80)⁵ [see *Clinical Studies (14.2)*].

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years for estrogen plus progestin compared with placebo.⁶ 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 estrogen plus progestin 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 estrogen plus progestin compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE (0.625) plus MPA (2.5mg) 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 [see *Clinical Studies (14.2)*].

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogens or among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy 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.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent nCI 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.⁷ In some epidemiologic studies, the use of estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies and some report no association.

5.4 Probable Dementia

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625mg) or placebo. In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625mg) plus MPA (2.5mg) or placebo.

In the WHIMS estrogen-alone ancillary study, 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 CE-alone vs. placebo was 1.49 (95 percent CI 0.83-2.66). The absolute risk of probable dementia for CE alone vs. placebo was 37 versus 25 cases per 10,000 women-years⁸ [see *Use in Specific Populations (8.5) and Clinical Studies (14.3)*].

In the WHIMS estrogen plus progestin ancillary study, after an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years⁸ [see *Use in Specific Populations (8.5) and Clinical Studies (14.3)*].

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent nCI 1.19-2.60). Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger women⁸ [see *Use in Specific Populations (8.5) and Clinical Studies (14.3)*].

5.5 Gallbladder Disease

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

5.6 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women 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.

5.7 Visual Abnormalities

Retinal vascular thrombosis has been reported in women 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.

5.8 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 an increased risk of breast cancer.

5.9 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.

5.10 Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis develops.

5.11 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women 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.

5.12 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women 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. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid hormone replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

5.13 Fluid Retention

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

5.14 Hypocalcemia

Estrogens should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

5.15 Exacerbation of Endometriosis

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

5.16 Exacerbation of Other Conditions

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

5.17 Effects on Barrier Contraception

No studies have been conducted to determine the potential for Synthetic Conjugated Estrogens, A Vaginal Cream to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber.

5.18 Laboratory Test Interactions

Serum follicle stimulating hormone and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy.

5.19 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. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG) and sex hormone binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

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

Impaired glucose tolerance.

6. ADVERSE REACTIONS

6.1 Clinical Study Experience

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 reactions that occurred in at least 3 percent of Synthetic Conjugated Estrogens, A Vaginal Cream 1g- and placebo-treated postmenopausal women in a 12-week, randomized, double-blind, placebo-controlled trial are shown in Table 1.

Table 1: Incidence of Treatment-Emergent Adverse Reactions with Greater than 3 percent Occurrence by Body System (Safety Cohort)

MedDra System Organ Class and Preferred Term	1 g SCE, A Vaginal Cream (N=150)		1g Placebo (N=155)	
	n	%	n	%
Infections and Infestations				
Vulvovaginal Mycotic Infection	7	4.7	5	3.2
Upper Respiratory Tract Infection	7	4.7	7	4.5
Nervous System Disorders				
Headache	6	4.0	0	0
Vascular Disorders				
Hot Flush	5	3.3	2	1.3

7. DRUG INTERACTIONS

No formal drug interactions studies have been conducted for Synthetic Conjugated Estrogens, A Vaginal Cream.

7.1 Metabolic 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 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 may result in adverse reactions.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Synthetic Conjugated Estrogens, A Vaginal Cream should not be used during pregnancy [see *Contraindications (4)*]. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8.3 Nursing Mothers

Synthetic Conjugated Estrogens, A Vaginal Cream, should not be used during lactation. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of mothers receiving estrogens. Caution should be exercised when Synthetic Conjugated Estrogens A, Vaginal Cream is administered to a nursing woman.

8.4 Pediatric Use

Synthetic Conjugated Estrogens, A Vaginal Cream is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Synthetic Conjugated Estrogens, A Vaginal Cream to determine whether those over 65 years of age differ from younger subjects in their response to synthetic conjugated estrogens, A.

The Women's Health Initiative Study

In the Women's Health Initiative (WHI) estrogen-alone substudy, there was a higher relative risk (daily CE [0.625mg] versus placebo) of stroke in women greater than 65 years of age [see *Clinical Studies (14.2)*].

In the WHI estrogen plus progestin substudy, there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age [see *Clinical Studies (14.2)*].

The Women's Health Initiative Memory Study

In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in the estrogen-alone and the estrogen plus progestin groups when compared to placebo [see *Clinical Studies (14.3)*].

Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women⁹ [see *Clinical Studies (14.3)*].

8.6 Renal Impairment

The effect of renal impairment on Synthetic Conjugated Estrogens, A Vaginal Cream pharmacokinetics has not been studied.

8.7 Hepatic Impairment

The effect of hepatic impairment on Synthetic Conjugated Estrogens, A Vaginal Cream pharmacokinetics has not been studied.

8.8 Gender

Synthetic Conjugated Estrogens, A Vaginal Cream is indicated for use in women only.

8.9 Race

No studies were done to determine the effect of race on the pharmacokinetics of Synthetic Conjugated Estrogens, A Vaginal Cream.

10. OVERDOSAGE

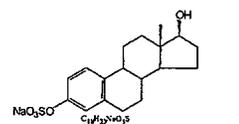
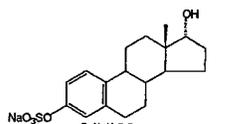
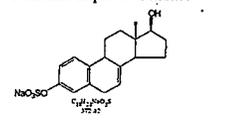
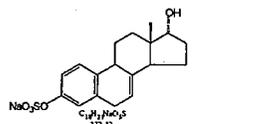
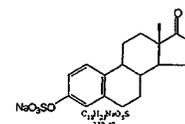
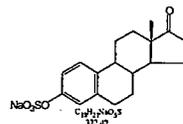
Overdosage of estrogen may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue and withdrawal bleeding in women. Treatment of overdose consists of discontinuation of Synthetic Conjugated Estrogens, A Vaginal Cream with institution of appropriate symptomatic care.

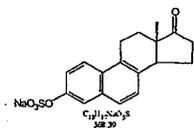
11. DESCRIPTION

Each gram of Synthetic Conjugated Estrogens, A Vaginal Cream contains 0.625 mg of synthetic conjugated estrogens, A in a non-liquefying base containing: benzyl alcohol, cetyl alcohol, cetyl esters wax, glycerin, glyceryl monostearate, light mineral oil, methyl stearate, propylene glycol monostearate, sodium hydroxide, sodium lauryl sulfate, sodium phosphate dibasic anhydrous, water and white wax.

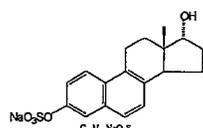
Synthetic conjugated estrogens, A, is the active ingredient in Synthetic Conjugated Estrogens, A Vaginal Cream and is a blend of nine (9) synthetic estrogenic substances. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17 α -dihydroequilin sulfate, sodium 17 α -estradiol sulfate, sodium 17 α -dihydroequilin sulfate, sodium 17 β -dihydroequilenin sulfate, sodium 17 β -dihydroequilenin sulfate, sodium 17 β -estradiol sulfate.

The structural formulae for these estrogens are:

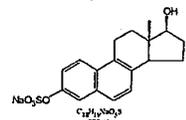




Sodium Equilenin Sulfate



Sodium 17α-Dihydroequilenin



Sodium 17β-Dihydroequilenin Sulfate

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 in postmenopausal women.

12.2 Pharmacodynamics

Currently, there are no pharmacodynamic data known for Synthetic Conjugated Estrogens, A Vaginal Cream.

12.3 Pharmacokinetics

Absorption

Pharmacokinetic parameters for baseline-adjusted (BA) free estrone, baseline-adjusted free estradiol, and free equilin at Day 1, Day 7 and Day 27 following the recommended dosing regimen of 1 gm Synthetic Conjugated Estrogens, A Vaginal Cream are presented in Table 2. The decline in plasma concentrations from Day 1 to Day 27 [see *Clinical Pharmacology, Excretion (12.4)*] suggests that there is very little to no systemic accumulation during this dosing interval for Synthetic Conjugated Estrogens, A Vaginal Cream.

Table 2: Pharmacokinetic parameters for baseline-adjusted free estrone, baseline-adjusted free estradiol, and free equilin at Day 1, Day 7 and Day 27 following the recommended dosing regimen of 1 gm Synthetic Conjugated Estrogens, A Vaginal Cream.

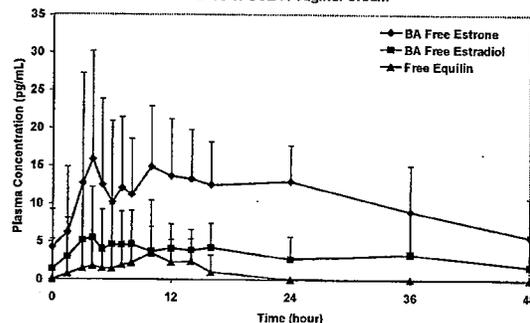
	BA Estrone	BA Estradiol	Equilin
Day 1			
C_{max} (pg/mL)	74.4	16.1	14.3
(%CV)	(87.7)	(84.8)	(92.3)
T_{max} (hr)	6.8	6.6	6.0
(%CV)	(74.1)	(61.7)	(64.8)
AUC_{0-24} (pg.hr/mL)	622.7	131.6	94.9
(%CV)	(64.4)	(56.9)	(93.4)
Day 7			
C_{max} (pg/mL)	38.5	12.7	7.4
(%CV)	(60.1)	(100.3)	(60.5)

T_{max} (hr)	8.3	8.9	10.1
(%CV)	(132.6)	(67.8)	(45.4)
AUC_{0-24} (pg.hr/mL)	560.7	139.7	65.4
(%CV)	(60.7)	(43.3)	(108.5)
Day 27			
C_{max} (pg/mL)	24.0	7.9	5.5
(%CV)	(47.8)	(92.4)	(125.4)
T_{max} (hr)	12.0	12.3	10.5
(%CV)	(72.7)	(80.1)	(40.0)
AUC_{0-24} (pg.hr/mL)	293.8	92.5	27.3
(%CV)	(46.3)	(89.1)	(135.8)

CV = coefficient of variation

The plasma concentration versus time profile for BA free estrone, BA free estradiol and free equilin at Day 27 following the recommended dosing regimen of 1 gm Synthetic Conjugated Estrogens, A Vaginal Cream is presented in Figure 1.

Figure 1: Pharmacokinetic Profiles of BA free Estrone, BA free Estradiol and free Equilin after Day 27 for Twice Weekly Dosing of 1g dose of SCE-A Vaginal Cream



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.

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. The vaginal delivery of estrogens circumvents first-pass metabolism. 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.

Excretion

After the recommended dosing application of Synthetic Conjugated Estrogens, A Vaginal Cream, the mean half-lives at steady-state were 22.1 hr for baseline-adjusted free estradiol, 34.1 hr for baseline-adjusted free estrone, and 15.7 hr for free equilin.

Specific Populations

No pharmacokinetic studies were conducted in specific populations, including patients with renal or hepatic impairment.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

14. CLINICAL STUDIES

14.1 Effects on Vulvar and Vaginal Atrophy

A 12-week prospective, randomized, double blind, placebo-controlled multicenter study was conducted to evaluate the efficacy and safety of Synthetic Conjugated Estrogens, A Vaginal Cream in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy in 275 (mean age = 59.9 years) naturally or surgically postmenopausal women between 42 and 76 years of age who at baseline had $\leq 5\%$ superficial cells on a vaginal smear, a vaginal pH >5.0 , and who identified their most bothersome moderate to severe symptom of vulvar and vaginal atrophy from among five symptoms (vaginal dryness, vaginal soreness, vaginal irritation/itching, pain during intercourse, bleeding after intercourse). The majority (86.5%) of the women were Caucasian (n=238), 6.5% were Hispanic (n=18), 5.4% were Black (n=15) and 0.7% were Asian (n=2). All patients were assessed for improvement in the mean change from baseline to Week 12 for the co-primary efficacy variables of: most bothersome symptom (MBS) of vulvar and vaginal atrophy (defined as the individual moderate to severe symptom that had been identified by the patient as most bothersome to her at baseline); percentage of vaginal superficial cells and percentage of vaginal parabasal cells on a vaginal smear, and vaginal pH.

In this study, a statistically significant mean reduction in severity between baseline and week 12 for the group treated with 1g Synthetic Conjugated Estrogens, A Vaginal Cream compared to placebo was observed for the symptoms of vaginal dryness and pain during intercourse when they were selected as the MBS (see Table 3).

Most Bothersome Symptom at Baseline	SCE, A Vaginal Cream 1 gram twice weekly	Placebo
Vaginal Dryness		
n	60	72
Baseline Severity*	2.58	2.47
Least Square Mean Change from Baseline (SE)	-1.65 (0.144)	-1.17 (0.130)
p-value versus Placebo	0.0016	NA
Pain With Intercourse		
N	45	41
Baseline Severity *	2.71	2.76
Least Square Mean Change from Baseline (SE)	-1.75 (0.208)	-0.82 (0.233)
p-value versus Placebo	0.0002	NA

SCE = synthetic conjugated estrogens

*severity was scored on a scale of 0 to 3 (0=none, 1=mild, 2=moderate and 3=severe)

In addition, Synthetic Conjugated Estrogens, A Vaginal Cream 1g increased superficial cells by a mean of 25.9 percent as compared to 3.8 percent for placebo (statistically significant). A corresponding statistically significant mean reduction from baseline in parabasal cells (36.3 percent for Synthetic Conjugated Estrogens, A Vaginal Cream and 5.7 percent for placebo) was observed at week 12. The mean reduction between baseline and week 12 in the pH was 1.47 in the Synthetic Conjugated Estrogens, A Vaginal Cream group and 0.30 in the placebo group (statistically significant).

14.2 Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625mg)-alone or in combination with MPA (2.5mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) defined as nonfatal myocardial infarction (MI), silent MI and CHD death], with invasive breast cancer as the primary adverse outcome, with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke,

pulmonary embolism (PE), endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone therapy in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other), after an average follow-up of 7.1 years are presented in Table 4.

Event	Relative Risk CE vs. Placebo (95% nCI*)	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events ^b	0.95 (0.78-1.16)	54	57
Nonfatal MI ^b	0.91 (0.73-1.14)	40	43
CHD death ^b	1.01 (0.71- 1.43)	16	16
All Stroke ^b	1.33 (1.05-1.68)	45	33
Ischemic ^b	1.55 (1.19-2.01)	38	25
Deep vein thrombosis ^{b,c}	1.47 (1.06-2.06)	23	15
Pulmonary embolism ^b	1.37 (0.90-2.07)	14	10
Invasive breast cancer ^b	0.80 (0.62-1.04)	28	34
Colorectal cancer ^d	1.08 (0.75-1.55)	17	16
Hip fracture ^b	0.65 (0.45-0.94)	12	19
Vertebral fractures ^{b,c}	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures ^{b,c}	0.58 (0.47-0.72)	35	59
Total fractures ^{b,e}	0.71 (0.64-0.80)	144	197
Death due to other causes ^{d,e}	1.08 (0.88-1.32)	53	50
Overall mortality ^{b,c}	1.04 (0.88-1.22)	79	75
Global index ^f	1.02 (0.92-1.13)	206	201

*Nominal confidence intervals unadjusted for multiple looks and multiple comparisons

^bResults are based on centrally adjudicated data for an average follow-up of 7.1 years

^cNot included in "Global Index"

^dResults are based on an average follow-up of 6.8 years

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

^fA subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures⁹. The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality [see Boxed Warnings, and Warnings and Precautions (5)].

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years¹ (see Table 3).

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined (see Table 4).¹⁰

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall-risk benefit profile. The WHI estrogen-

alone substudy stratified by age showed in women 50-59 years of age, a non-significant trend toward reduced risk for CHD [HR 0.63 (95 percent CI 0.36-1.09)] and overall mortality [HR 0.71 (95 percent CI 0.46-1.11)].

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was also stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 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[¶].

Results of the estrogen-plus-progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 5 below. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Event	Relative Risk CE/MPA vs. Placebo (95% nCI ^b)	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99-1.53)	41	34
Non-fatal MI ^b	1.28 (1.00-1.63)	31	25
CHD death	1.10 (0.70-1.75)	8	8
All strokes	1.31 (1.03-1.68)	33	25
Ischemic stroke	1.44 (1.09-1.90)	26	18
Deep vein thrombosis ^c	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer ^d	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer ^e	0.81 (0.48-1.36)	6	7
Cervical cancer ^e	1.44 (0.47-4.42)	2	1
Hip fracture ^e	0.67 (0.47-0.96)	11	16
Vertebral fractures ^e	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures ^e	0.71 (0.59-0.85)	44	62
Total fractures ^e	0.76 (0.69-0.83)	152	199
Overall Mortality [¶]	1.00 (0.83-1.19)	52	52
Global Index [¶]	1.13 (1.02-1.25)	184	165

* Results are based on centrally adjudicated data.

^b Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

^c Not included in Global Index

^d Includes metastatic and non-metastatic breast cancer, with the exception of *in situ* cancer

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

[¶] 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, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50-59 years of age, a non-significant trend toward reduced risk for overall mortality [HR 0.69 (95 percent CI 0.44-1.07)].

14.3 Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 years to 79 years of age and older (45 percent, age 65 to 69 years; 36 percent, 70 to 74 years; 19 percent, 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment and placebo groups was AD. Since the ancillary study was conducted in women 65 to 79 years of age it is unknown whether these findings apply to younger postmenopausal women [see *Warnings and Precautions (5.4) and Use in Specific Populations (8.5)*].

The WHIMS estrogen plus progestin ancillary study enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent, age 65 to 69 years; 35 percent, 70 to 74 years; 18 percent, 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE (0.625) plus MPA (2.5mg) versus placebo was 2.05 (95 percent CI 1.21-3.48). The absolute risk of probable dementia for CE (0.625) plus MPA (2.5mg) versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease, vascular dementia and mixed types (having features of both AD and VaD). The most common classification of probable dementia in both the treatment and placebo groups was AD. The most common classification of probable dementia in the treatment group and placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see *Warnings and Precautions (5.4) and Use in Specific Population (8.5)*].

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women [see *Warnings and Precautions (5.4) and Use in Specific Populations (8.5)*].

15. REFERENCES

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- Jackson RD, et al. Effects of Conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. *J Bone Miner Res*. 2006;21:817-828.
- Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation*. 2006;113:2425-2434.

16. HOW SUPPLIED/STORAGE AND HANDLING

Synthetic Conjugated Estrogens, A (synthetic conjugated estrogens, A) Vaginal Cream 0.625 mg/g is available in a tube containing 30 g cream with eight (8) re-usable applicators:

NDC 51285-586-30

Store at 20-25°C (68-77°F); excursions are permitted to 15-30°C (59-86°F). Do not freeze.

17. PATIENT COUNSELING INFORMATION

See 17.4 for FDA-Approved Patient Labeling

17.1 Vaginal Bleeding

Inform postmenopausal women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible [see *Warnings and Precautions* (5.3)].

17.2 Possible Serious Adverse Reactions with Estrogens

Inform postmenopausal women of possible serious adverse reactions of estrogen therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia [see *Warnings and Precautions* (5.2, 5.3, 5.4)].

17.3 Possible Less Serious But Common Adverse Reactions with Estrogens

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen therapy such as headache, breast pain and tenderness, nausea and vomiting.

17.4 Instructions for Use of Vaginal Applicator

1. Remove cap from tube.
2. Screw nozzle end of applicator onto tube.
3. Gently squeeze tube from the bottom to force sufficient cream into the applicator to the marked stopping point on the applicator as a guide to measure the correct dose.
4. Unscrew applicator from tube.
5. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position.

TO CLEANSE APPLICATOR: Pull plunger to remove it from barrel. Wash with mild soap and warm water.

DO NOT BOIL OR USE HOT WATER.

17.5 FDA-Approved Patient Labeling

PATIENT INFORMATION

Synthetic Conjugated Estrogens, A Vaginal Cream

Read this PATIENT INFORMATION before you start using Synthetic Conjugated Estrogens, A Vaginal Cream and read what you get each time you refill your Synthetic Conjugated Estrogens, A Vaginal Cream Prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms and their treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT Synthetic Conjugated Estrogens, A Vaginal Cream (SYNTHETIC ESTROGEN MIXTURE)?

- Estrogens increase the chances of getting cancer of the uterus.
- Report any unusual vaginal bleeding right away while you are taking Synthetic Conjugated Estrogens, A Vaginal Cream. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare 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, strokes or dementia.
- Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens, with or without progestins may increase your risk of dementia based on a study of women age 65 years or older. You and your healthcare provider should talk regularly about whether you still need treatment with Synthetic Conjugated Estrogens, A Vaginal Cream.

What is Synthetic Conjugated Estrogens, A Vaginal Cream?

Synthetic Conjugated Estrogens, A Vaginal Cream is a medicine that contains a mixture of synthetic estrogens.

What is Synthetic Conjugated Estrogens, A Vaginal Cream used for?

Synthetic Conjugated Estrogens, A Vaginal Cream is used after menopause to:

- Treat dryness in and around the vagina caused by menopausal changes of the vagina
- Treat painful intercourse caused by menopausal changes of the vagina

You and your healthcare provider should talk regularly about whether you still need treatment with Synthetic Conjugated Estrogens, A Vaginal Cream to control these problems.

Who should not use Synthetic Conjugated Estrogens, A Vaginal Cream?

Do not start using Synthetic Conjugated Estrogens, A Vaginal Cream 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 have had cancer, talk with your healthcare provider about whether you should use Synthetic Conjugated Estrogens, A Vaginal Cream.
- Had a stroke or heart attack
- Currently have or have had blood clots
- Currently have or have had liver problems
- Are allergic to Synthetic Conjugated Estrogens, A Vaginal Cream or any of its ingredients

See the end of this leaflet for a list of ingredients in Synthetic Conjugated Estrogens, A Vaginal Cream.

- Think you may be pregnant

Tell your healthcare provider:

- If you have any unusual vaginal bleeding.
Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find the cause.
- About all of your medical problems.
Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, 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.
This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Synthetic Conjugated Estrogens, A Vaginal Cream works. Synthetic Conjugated Estrogens, A Vaginal Cream 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 using Synthetic Conjugated Estrogens, A Vaginal Cream.
- If you are breast feeding.
The hormones in Synthetic Conjugated Estrogens, A Vaginal Cream can pass into your milk.

How should I use Synthetic Conjugated Estrogens, A Vaginal Cream
Synthetic Conjugated Estrogens, A is a cream that you place in your vagina with an applicator.

1. Take the dose recommended by your health care provider and talk to him or her 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. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Synthetic Conjugated Estrogens, A Vaginal Cream.

INSTRUCTIONS FOR USE

1. Remove cap from tube.
2. Screw nozzle end of applicator onto tube.
3. Gently squeeze tube from the bottom to force sufficient cream into the applicator to the marked stopping point on the applicator as a guide to measure the correct dose.
4. Unscrew applicator from tube.
5. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position.

TO CLEANSE APPLICATOR: Pull plunger to remove it from barrel. Wash with mild soap and warm water.

DO NOT BOIL OR USE HOT WATER.

What are the possible side effects of Synthetic Conjugated Estrogens, A Vaginal Cream?

Synthetic Conjugated Estrogens, A Vaginal Cream is only used in and around the vagina; however, the risks associated with oral estrogens should be taken into account.

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious but less common side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer
- High blood pressure
- Liver problems
- High blood sugar
- Enlargement of benign tumors of the uterus ("fibroids")

Some of the warning signs of these 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
- Yellowing of skin, eyes, or nail beds

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

Less serious but common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection
- Reactions from inserting Synthetic Conjugated Estrogens, A Vaginal Cream, such as vaginal burning, irritation, and itching

These are not all the possible side effects of Synthetic Conjugated Estrogens, A Vaginal Cream. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with Synthetic Conjugated Estrogens, ATM Vaginal Cream?

- Talk with your healthcare provider regularly about whether you should continue using Synthetic Conjugated Estrogens, A Vaginal Cream.
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. The addition of a progestin is generally 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 taking Synthetic Conjugated Estrogens, A Vaginal Cream.

- Have a pelvic exam, 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 Synthetic Conjugated Estrogens, A Vaginal Cream.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Synthetic Conjugated Estrogens, A Vaginal Cream for conditions for which it was not prescribed. Do not give Synthetic Conjugated Estrogens, A Vaginal Cream to other people, even if they have the same symptoms you have. It may harm them. **Keep Synthetic Conjugated Estrogens, A Vaginal Cream out of the reach of children.**

It is not known whether or not Synthetic Conjugated Estrogens, A Vaginal Cream can weaken or contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber.

This leaflet provides a summary of the most important information about Synthetic Conjugated Estrogens, A Vaginal Cream. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Synthetic Conjugated Estrogens, A Vaginal Cream that is written for health professionals. You can get more information by calling the toll free number 1-800-227-7522.

What are the inactive ingredients in Synthetic Conjugated Estrogens, A Vaginal Cream?

The ingredients are: benzyl alcohol, cetyl alcohol, cetyl esters wax, glycerin, glyceryl monostearate, light mineral oil, methyl stearate, propylene glycol monostearate, sodium hydroxide, sodium lauryl sulfate, sodium phosphate dibasic anhydrous, water, and white wax.

Store at 20-25°C (68-77°F); excursions are permitted to 15-30°C (59-86°F). **Do not freeze.**

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