

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ESTRASORB® safely and effectively. See full prescribing information for ESTRASORB®.

ESTRASORB® (estradiol topical emulsion) for topical use
Initial U.S. Approval: 1975

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA, and BREAST CANCER

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.1)
- The WHI 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 (5.3)
- Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia (5.1, 5.3).

Estrogen Plus Progestin Therapy

- The WHI estrogen plus progestin substudy reported increased risks of pulmonary embolism (PE), DVT, stroke, and myocardial infarction (MI) (5.1)
- The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)
- 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 (5.3)
- Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia (5.1, 5.3).

RECENT MAJOR CHANGES

Boxed Warning 9/2024

Warnings and Precautions, Malignant Neoplasms (5.2) 12/2023

INDICATIONS AND USAGE

- ESTRASORB is an estrogen indicated for the treatment of moderate to severe vasomotor symptoms due to menopause (1.1)

DOSAGE AND ADMINISTRATION

- Apply one pouch to the left thigh and calf and one pouch to the right thigh and calf each morning (2.1)

DOSAGE FORM AND STRENGTHS

- Pouch: 1.74 grams of emulsion containing 2.5 mg estradiol per gram of emulsion (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4, 5.2)
- Breast cancer or history of breast cancer (4, 5.2)
- Estrogen-dependent neoplasm (4, 5.2)
- Active DVT, PE, or history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke or MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction, angioedema, or hypersensitivity to ESTRASORB (4)
- Hepatic impairment or disease (4, 5.10)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogens if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid hormone replacement therapy (5.11, 5.19)

ADVERSE REACTIONS

The most common adverse reactions with ESTRASORB (incidence ≥ 5 percent) are: endometrial disorder, infection, breast pain, headache, sinusitis, and pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Exeltis USA, Inc. at 1-877-324-9349 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 and decrease or increase estrogen plasma concentrations. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2024

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FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA, and BREAST CANCER

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 progestogen to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in postmenopausal women with undiagnosed, persistent or recurring abnormal genital bleeding [*see Warnings and Precautions (5.2)*].

Cardiovascular Disorders and Probable Dementia

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]-alone, relative to placebo [*see Warnings and Precautions (5.1), and Clinical Studies (14.2)*].

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age and 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 (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.3)*].

Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia [*see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.2, 14.3)*].

Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

The WHI estrogen plus progestin substudy reported increased risks of pulmonary embolism (PE), DVT, stroke, and myocardial infarction (MI) 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 (5.1), and Clinical Studies (14.3)*].

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 and 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* (5.3), *Use in Specific Populations* (8.5), and *Clinical Studies* (14.3)].

Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia [see *Warnings and Precautions* (5.1, 5.3), and *Clinical Studies* (14.2, 14.3)].

Breast Cancer

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer [see *Warnings and Precautions* (5.2), and *Clinical Studies* (14.3)].

Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen product is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestogen therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

2 DOSAGE AND ADMINISTRATION

For topical use only. ESTRASORB is not for ophthalmic, oral, or intravaginal use. ESTRASORB should not be applied to the face or breasts.

Generally, when estrogen therapy is prescribed for a postmenopausal woman with a uterus, consider addition of a progestogen to reduce the risk of endometrial cancer. Generally, a woman without a uterus does not need to use a progestogen in addition to her estrogen therapy. In some cases, however, hysterectomized women who have a history of endometriosis may need a progestogen [see *Warnings and Precautions* (5.2, 5.14)].

Use estrogen-alone, or in combination with a progestogen, at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Re-evaluate postmenopausal women periodically as clinically appropriate to determine if treatment is still necessary.

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

The single approved dose of ESTRASORB is 3.48 grams daily. Apply one pouch (1.74 grams) to the left thigh and calf and one pouch (1.74 grams) to the right thigh and calf each morning. Re-evaluate postmenopausal women periodically as clinically appropriate to determine if treatment is still necessary.

The lowest effective dose of ESTRASORB for this indication has not been determined.

3 DOSAGE FORMS AND STRENGTHS

ESTRASORB is available in a pouch. Each pouch contains 1.74 grams of ESTRASORB. Each gram of ESTRASORB contains 2.5 mg estradiol.

4 CONTRAINDICATIONS

ESTRASORB is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding [see *Warnings and Precautions* (5.2)].
- Breast cancer or a history of breast cancer [see *Warnings and Precautions* (5.2)].
- Estrogen-dependent neoplasia [see *Warnings and Precautions* (5.2)].
- Active DVT, PE, or history of these conditions [see *Warnings and Precautions* (5.1)].
- Active arterial thromboembolic disease (for example, stroke or MI), or a history of these conditions. [see *Warnings and Precautions* (5.1)].
- Known anaphylactic reaction, angioedema, or hypersensitivity to ESTRASORB.
- Hepatic impairment or disease.
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

Increased risks of stroke and DVT are reported with estrogen-alone therapy. Increased risks of PE, DVT, stroke and MI are reported with estrogen plus progestin therapy. Immediately discontinue estrogen with or without progestogen therapy if any of these occur or are suspected.

Manage appropriately any risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus).

Stroke

The WHI estrogen-alone substudy reported a statistically significant increased risk of stroke in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 strokes per 10,000 women-years, respectively). The increase in risk was demonstrated in year 1 and persisted [see *Clinical Studies* (14.2)]. Immediately discontinue estrogen-alone therapy if a stroke occurs or is suspected.

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

The WHI estrogen plus progestin substudy reported a statistically significant increased risk of stroke in women 50 to 79 years of age receiving CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 strokes per 10,000 women-years, respectively) [see *Clinical Studies* (14.2)]. The increase in risk was demonstrated after the first year and persisted¹. Immediately discontinue estrogen with or without progestogen therapy if a stroke occurs or is suspected.

Coronary Heart Disease

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

Subgroup analyses of women 50 to 59 years of age, who were less than 10 years since menopause, suggest a reduction (not statistically significant) in CHD events in those women receiving CE (0.625 mg)-alone compared to placebo (8 versus 16 per 10,000 women-years).¹

The WHI estrogen plus progestin substudy reported an increased risk (not statistically significant) of CHD events in those women receiving daily CE (0.625 mg) plus MPA (2.5 mg) 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 66.7 years of age, 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 CHD. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the 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/ plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE), was increased for women receiving daily CE (0.625 mg)-alone 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)*]. Immediately discontinue estrogen-alone therapy if a VTE occurs or is suspected.

The WHI estrogen plus progestin substudy reported a statistically significant 2-fold greater rate of VTE in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted⁴ [see *Clinical Studies (14.2)*]. Immediately discontinue estrogen plus progestogen therapy if a VTE occurs or is suspected.

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

5.2 Malignant Neoplasms

Endometrial Cancer

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

Clinical surveillance of all women using estrogen-alone or estrogen plus progestogen therapy is important. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in postmenopausal women with persistent or recurring abnormal vaginal bleeding with unknown etiology. 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 progestogen to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80)⁵ [see *Clinical Studies (14.2)*].

After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive 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 CE plus 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 plus 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 plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) 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 groups⁶ [see *Clinical Studies (14.2)*].

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer with estrogen plus progestin therapy, and a smaller increase in the risk for breast cancer with estrogen-alone therapy, after several years of use. One large meta-analysis of prospective cohort studies reported increased risks that were dependent upon duration of use and could last up to >10 years after discontinuation of estrogen plus progestin therapy and estrogen-alone therapy. Extension of the WHI trials also demonstrated increased breast cancer risk associated with estrogen plus progestin therapy. 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. These studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and 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.

Ovarian Cancer

The CE plus MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24), but it was not statistically significant. The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.⁷

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 - 1.50); there was no difference in the risk estimates by duration of the expose (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

5.3 Probable Dementia

In the WHI Memory Study (WHIMS) estrogen-alone ancillary study, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

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 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-years⁸ [see *Use in Specific Populations (8.5)*, and *Clinical Studies (14.3)*].

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 (0.625 mg) plus MPA (2.5 mg) or placebo.

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 in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies 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). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women⁸ [see *Use in Specific Populations (8.5)*, and *Clinical Studies (14.3)*].

5.4 Gallbladder Disease

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

5.5 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. Discontinue estrogens, including ESTRASORB if hypercalcemia occurs, and take appropriate measures to reduce the serum calcium level.

5.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue ESTRASORB pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Permanently discontinue estrogens, including ESTRASORB, if examination reveals papilledema or retinal vascular lesions.

5.7 Addition of a Progestogen When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestogen for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lower 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 progestogens with estrogens compared to estrogen-alone treatment. These include an increased risk of breast cancer.

5.8 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.

5.9 Exacerbation of Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Discontinue ESTRASORB if pancreatitis occurs.

5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with hepatic impairment. Exercise caution in any woman with a history of cholestatic jaundice associated with past estrogen use or with pregnancy. In the case of recurrence of cholestatic jaundice, discontinue ESTRASORB.

5.11 Exacerbation of 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 replacement therapy. Monitor thyroid function in these women during treatment with ESTRASORB to maintain their free thyroid hormone levels in an acceptable range.

5.12 Fluid Retention

Estrogens may cause some degree of fluid retention. Monitor any woman with a condition(s) that might predispose her to fluid retention, such as cardiac or renal impairment. Discontinue estrogen-alone therapy, including ESTRASORB, with evidence of medically concerning fluid retention.

5.13 Hypocalcemia

Estrogen-induced hypocalcemia may occur in women with hypoparathyroidism. Consider whether the benefits of estrogen therapy, including ESTRASORB, outweigh the risks in such women.

5.14 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. Consider the addition of progestogen therapy for women known to have residual endometriosis post-hysterectomy.

5.15 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. Consider whether the benefits of estrogen therapy, including ESTRASORB, outweigh the risks in such women.

5.16 Exacerbation of Other Conditions

Estrogen therapy, including ESTRASORB, may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas. Consider whether the benefits of estrogen therapy outweigh the risks in women with such conditions.

5.17 Application of Sunscreen

Estradiol absorption was increased when sunscreen was applied 10 minutes before ESTRASORB application. Estradiol absorption was also increased when sunscreen was applied 25 minutes after ESTRASORB application [*see Clinical Pharmacology (12.3)*].

5.18 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol concentrations have not been shown to be useful in the management of postmenopausal women with moderate to severe vasomotor symptoms.

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 TBG 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 high-density lipoprotein (HDL) and HDL-2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, and increased triglycerides levels.
- Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

- Cardiovascular Disorders [*see Boxed Warning, Warning and Precautions (5.1)*].

- Malignant Neoplasms [see Boxed Warning, Warnings and Precautions (5.2)].

6.1 Clinical Trials 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.

Table 1 summarizes the treatment-emergent adverse reactions with ESTRASORB therapy.

Table 1: Number (%) of Patients Reporting ≥5% Treatment-Emergent Adverse Reactions			
Body system/ Preferred term	Statistic	Placebo (n = 134)	ESTRASORB 3.45 grams (n = 139)
Number of subjects with ≥1 TEAE	n (%)	82 (61)	95 (68)
Body as a whole	n (%)	40 (30)	49 (35)
Headache	n (%)	17 (13)	12 (9)
Infection	n (%)	10 (7)	16 (12)
Respiratory	n (%)	15 (11)	19 (14)
Sinusitis	n (%)	6 (4)	9 (6)
Skin and appendages	n (%)	7 (5)	15 (11)
Pruritus	n (%)	0	5 (4)
Urogenital	n (%)	20 (15)	44 (32)
Breast pain	n (%)	4 (3)	14 (10)
Endometrial disorder	n (%)	11 (8)	21 (15)

TEAE = Treatment-emergent adverse event.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ESTRASORB. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary system

Unusual 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.

Breasts

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

Cardiovascular

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

Gastrointestinal

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

Skin

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

Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

Central Nervous System

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

Miscellaneous

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

7 DRUG INTERACTIONS

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, and 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

Risk Summary

ESTRASORB is not indicated for use in pregnancy. There are no data with the use of ESTRASORB in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies or limb-reduction defects) following exposure to combined hormonal contraceptives (estrogens and progestins) before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

Estrogens are present in human milk and can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ESTRASORB and any potential adverse effects on the breastfed child from ESTRASORB or from the underlying maternal condition.

8.4 Pediatric Use

ESTRASORB is not indicated for use in pediatric patients. 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 ESTRASORB to determine whether those over 65 years of age differ from younger subjects in their response to ESTRASORB.

The Women's Health Initiative Studies

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

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), 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 WHIMS, ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo [see *Warnings and Precautions* (5.3), and *Clinical Studies* (14.3)].

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women⁸ [see *Warnings and Precautions* (5.3), and *Clinical Studies* (14.3)].

10 OVERDOSAGE

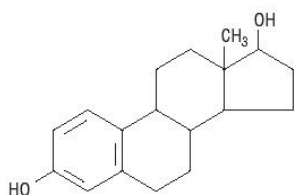
Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of ESTRASORB therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

ESTRASORB (estradiol topical emulsion) is designed to deliver estradiol to the blood circulation following topical application of an emulsion. Each gram of ESTRASORB contains 2.5 mg of estradiol hemihydrate USP, EP, which is encapsulated using a micellar nanoparticle technology. ESTRASORB is packaged in foil pouches containing 1.74 grams of drug product. Daily topical application of the contents of two foil pouches provides systemic delivery of 0.05 mg of estradiol per day.

Estradiol hemihydrate USP, EP (estradiol) is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3, 17 β -diol, hemihydrate. The molecular formula of estradiol hemihydrate is C₁₈H₂₄O₂ • 1/2 H₂O, and the molecular weight is 281.4 g/mol.

The structural formula is:



The active ingredient in ESTRASORB is estradiol. The remaining components (soybean oil, water, polysorbate 80, and ethanol) are pharmacologically inactive.

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 in the peripheral tissues. Thus, estrone and its 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.

12.2 Pharmacodynamics

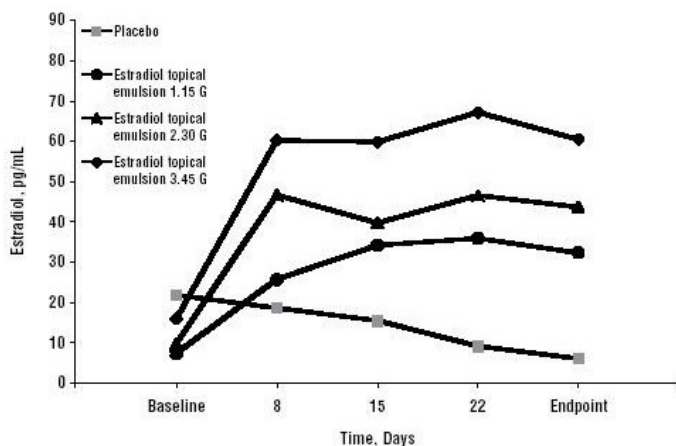
Generally, a serum estrogen concentration does not predict an individual woman's therapeutic response to ESTRASORB nor her risk for adverse outcomes. Likewise, exposure comparisons across different estrogen products to infer efficacy or safety for the individual woman may not be valid.

12.3 Pharmacokinetics

Absorption

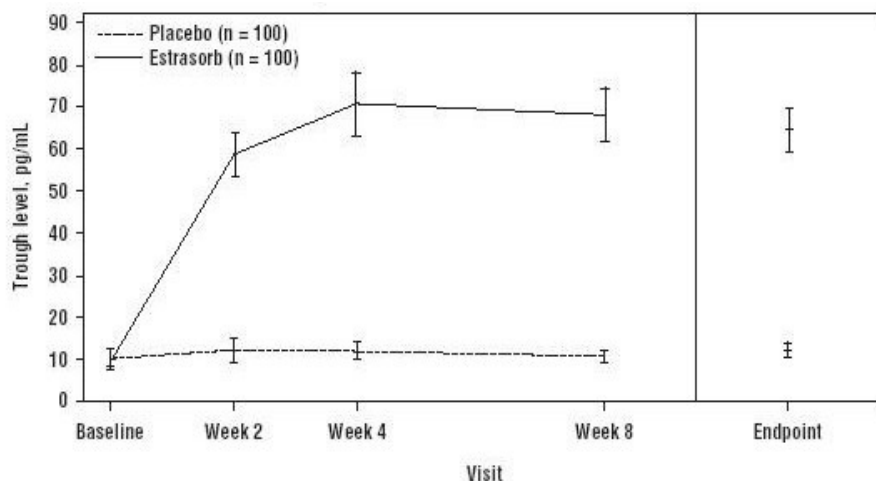
In a multiple-dose study, 125 women were treated for 28 days once daily with placebo or ESTRASORB containing 2.875 mg, 5.75 mg, or 8.625 mg of estradiol. The mean change from baseline in serum estradiol concentrations increased in a dose-dependent manner compared with placebo (Figure 1 below).

Figure 1. Mean serum estradiol concentrations (pg/mL) following topical application of placebo or ESTRASORB containing 2.875 mg, 5.75 mg, 8.625 mg of estradiol



Serum estradiol concentrations were also assessed in a second study involving 200 postmenopausal women, who applied either a daily dose of ESTRASORB (containing 8.625 mg of estradiol; n = 100) or placebo (n = 100) for 12 weeks. Trough estradiol concentrations in the ESTRASORB treatment group increased from a mean of 8.9 pg/mL at baseline to 58.6 pg/mL and 70.2 pg/mL at Weeks 2 and 4, respectively (Figure 2). Trough levels of ESTRASORB remained at a plateau throughout the rest of the study: 67.3 pg/mL at Week 8 and 63.0 pg/mL at the end of the study.

Figure 2: Mean (SE) Trough Serum Estradiol Concentrations Following Daily Topical Application of 3.45 Grams of ESTRASORB Containing 2.5 mg of Estradiol per Gram for 12 weeks.



SE = Standard error of the mean

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. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestines, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

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

Application of Sunscreen

Application of SPF15 sunscreen 10 minutes prior to the application of ESTRASORB containing 8.7 mg of estradiol increased the exposure to estradiol by approximately 38%. When SPF15 sunscreen is applied 25 minutes after the application of ESTRASORB containing 8.7 mg of estradiol, the increase in exposure to estradiol was approximately 46%.

Potential for Estradiol Transfer

Estradiol was detected on the skin at 2 and 8 hours post-application. Washing the application area with soap and water 8 hours post-application removed detectable estradiol from the application site.

Upon physical contact made by adult males for 2 minutes to the thighs of females who received daily doses of ESTRASORB containing 8.7 mg of estradiol over a two day period at 2 and 8 hours post-application in a separate study, a mean increase of approximately 25 percent in serum estradiol exposure was identified [see *Dosage and Administration* (2)].

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 Vasomotor Symptoms in Postmenopausal Women

In a 12-week randomized, placebo-controlled clinical trial, a total of 200 postmenopausal women (average 52 years of age, range 46 to 58, 79 percent Caucasian in the ESTRASORB treatment group; average 51.8 years of age, range 45.8 to 57.8, 72 percent Caucasian in the placebo treatment group) were assigned to receive ESTRASORB (3.45 grams containing 2.5 mg of estradiol per gram) or placebo for a 12-week duration. ESTRASORB was shown to be statistically better than placebo at Weeks 4 and 12 for relief of both the frequency and severity of moderate to severe vasomotor symptoms (p-value <0.001 for Weeks 4 and 12). Frequency results are shown in Table 2. Severity results are shown in Table 3.

Table 2. Mean Number and Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms Per Day (Intent-to-Treat Population)			
Time point		Treatment Group	
		Placebo	ESTRASORB
Baseline (observed value)		(N = 100)	(N = 100)
Mean Number of Hot Flushes (SD)		13.63 (5.48)	13.05 (5.78)
Week 4		(N = 97)	(N = 96)
Mean Number of Hot Flushes (SD)		7.46 (6.42)	4.42 (5.60)
Mean Change from Baseline (SD)		-5.97 (4.76)	-8.56 (6.19)
P-value vs. Placebo		NA	<0.001
Week 12		(N = 90)	(N = 90)
Mean Number of Hot Flushes (SD)		5.88 (6.17)	2.00 (3.64)
Mean Change from Baseline (SD)		-7.20 (5.39)	-11.11 (6.84)
P-value vs. Placebo		NA	<0.001

SD = Standard Deviation; NA = Not applicable

Table 3. Mean Change from Baseline in the Severity Score^a of Hot Flushes Per Day, Intent-to-Treat Population, Most Recent Value Carried Forward			
Time point		Treatment Group	
		Placebo	ESTRASORB
Baseline (observed value)		(N = 100)	(N = 100)
Mean Severity Score per Day (SD)		2.44 (0.37)	2.36 (0.36)
Week 4		(N = 97)	(N = 96)
Mean Severity Score per Day (SD)		1.99 (0.81)	1.47 (1.03)
Mean Change from Baseline (SD)		-0.45 (0.75)	-0.89 (1.04)
P-value vs. Placebo		NA	<0.001
Week 12		(N = 90)	(N = 90)
Mean Severity Score per Day (SD)		1.88 (0.98)	0.92 (1.00)
Mean Change from Baseline (SD)		-0.55 (0.91)	-1.44 (1.04)
P-value vs. Placebo		NA	<0.001

SD = Standard Deviation; NA = Not applicable

^a The severity score per day is determined by calculating the sum of recorded daily severity and dividing this number by the total number of hot flushes on that day.

14.2 Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A “global index” included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other cause. These substudies did not evaluate the effects of CE-alone 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 in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, 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.

Table 4. Relative and Absolute Risk Seen in the Estrogen Alone Substudy of WHI^a

Event	Relative Risk CE vs. Placebo (95% nCI ^b)	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events ^c	0.95 (0.78–1.16)	54	57
Non-fatal MI ^c	0.91 (0.73–1.14)	40	43
CHD death ^c	1.01 (0.71–1.43)	16	16
All strokes ^c	1.33 (1.15–1.68)	45	33
Ischemic stroke ^c	1.55 (1.19–2.01)	38	25
Deep vein thrombosis ^{c,d}	1.47 (1.06–2.06)	23	15
Pulmonary embolism ^c	1.37 (0.90–2.07)	14	10
Invasive breast cancer ^c	0.80 (0.62–1.04)	28	34
Colorectal cancer ^c	1.08 (0.75–1.55)	17	16
Hip fracture ^c	0.65 (0.45–0.94)	12	19
Vertebral fractures ^{c,d}	0.64 (0.44–0.93)	11	18
Lower arm/wrist fractures ^{c,d}	0.58 (0.47–0.72)	35	59
Total fractures ^{c,d}	0.71 (0.64–0.80)	144	197
Death due to other causes ^{e,f}	1.08 (0.88–1.32)	53	50
Overall mortality ^{c,d}	1.04 (0.88–1.22)	79	75
Global Index ^g	1.02 (0.92–1.13)	206	201

^a Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

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

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

^d Not included in “global index”.

^e Results are based on an average follow-up of 6.8 years.

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

^g A subset of the events was combined in a “global index”, defined as the earliest occurrence of CHD events: invasive breast cancer, stroke, PE, endometrial cancer, 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.

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 to placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant differences 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.¹⁰

Timing of the initiation of estrogen-alone 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 to 59 years of age a non-significant trend toward reduced risk for CHD [hazard ratio (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 stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive 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 reduction 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. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 5. Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years^{a,b}

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

^a Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

^b Results are based on centrally adjudicated data.

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

^d Not included in “global index”.

^e Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.

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

^g 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.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified for age showed in women 50 to 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 WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45 percent were 65 to 69 years of age, 36 percent were 70 to

74 years of age, and 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone 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 type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the 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* (5.3), and *Use in Specific Populations* (8.5)].

The WHIMS estrogen plus progestin ancillary study enrolled 4532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age, 35 percent were 70 to 74 years of age, and 18 percent were 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 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 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the 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* (5.3), and *Use in Specific Populations* (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* (5.3), and *Use in Specific Populations* (8.5)].

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ESTRASORB (estradiol topical emulsion), nominal 0.05 mg/day:

ESTRASORB is packaged in foil-laminated pouches. A daily dose of ESTRASORB is two foil-laminated pouches. Each pouch contains 1.74-grams. Each 1.74-gram, foil-laminated pouch contains 4.35 mg of estradiol hemihydrate USP, EP. Each box of ESTRASORB contains fourteen 1.74-gram, foil-laminated pouches.

1-month supply carton of 56 pouches, NDC 0642-7465-56

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 40°C (59°F to 104°F).

17 PATIENT COUNSELING INFORMATION

Advise women to read the FDA-approved patient labeling (Patient information and Instructions for Use)

Vaginal Bleeding

Inform postmenopausal women to report any vaginal bleeding to their healthcare providers as soon as possible [*see Warnings and Precautions (5.2)*].

Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia [*see Warnings and Precautions (5.1, 5.2, 5.3)*].

Possible Common Adverse Reactions of Estrogen-Alone Therapy

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

Patient Information

ESTRASORB[®] (*es-truh-sawrb*)
(estradiol topical emulsion)

Read this Patient Information before you start using ESTRASORB and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about ESTRASORB (an estrogen hormone)?

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb).
- Report any unusual vaginal bleeding right away while you are using ESTRASORB. 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 estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline of brain function).
- Using estrogen-alone may increase your chances of getting strokes or blood clots.
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age and older.
- Do not use estrogens with progestogens to prevent heart disease, heart attacks, strokes or dementia.
- Using estrogens with progestogens may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestogens may increase your chance of getting dementia, based on a study of women 65 years of age and older.
- Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, blood clots, and dementia. Only one estrogen with progestogen product and dose have been shown to increase your chances of getting heart attacks, strokes, breast cancer, blood clots, and dementia. Because other products and doses have not been studied in the same way, it is not known how the use of ESTRASORB will affect your chances of these conditions. You and your healthcare provider should talk regularly about whether you still need treatment with ESTRASORB.

What is ESTRASORB?

ESTRASORB is a prescription medicine that contains estradiol (an estrogen hormone). When applied to the skin, estradiol is absorbed through the skin into the bloodstream.

What is ESTRASORB used for?

ESTRASORB 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 and 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 estrogen levels begin dropping, some women get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need to use estrogens. In other women, symptoms can be more severe.

Who should not use ESTRASORB?

Do not start using ESTRASORB if you:

- **have 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 out the cause.

- **have been diagnosed with a bleeding disorder**
- **currently have or have had certain cancers**

Estrogens may increase the chances of getting certain types of cancer, including cancer of the breast or uterus (womb). If you have or have had cancer, talk with your healthcare provider about whether you should use ESTRASORB.

- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**

- **are allergic to ESTRASORB or any of its ingredients**

See the list of ingredients in ESTRASORB at the end of this leaflet.

Before you use ESTRASORB, tell your healthcare provider about all of your medical conditions, including 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 out the cause.

- **have any other medical conditions that may become worse while you are using ESTRASORB**

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, angioedema (swelling of face or tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **are going to have surgery or will be on bed rest**

Your healthcare provider will let you know if you need to stop using ESTRASORB.

- **are pregnant or think you may be pregnant**

ESTRASORB is not for pregnant women.

- **are breastfeeding**

The hormone in ESTRASORB can pass into your breast milk.

Tell your healthcare provider about all the medicine you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Some medicines may affect how ESTRASORB works. Some other medicines and food products may increase or decrease the concentration of the hormone in ESTRASORB in the blood. ESTRASORB may affect how your other medicines work. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get new medicine.

How should I use ESTRASORB?

See the “Instructions for Use” at the end of this Patient Information.

- Use ESTRASORB exactly as your healthcare provider tells you to use it.
- ESTRASORB is for skin use only. **Do not** apply ESTRASORB to your face or to your breasts.
- Apply ESTRASORB to clean, dry skin on both legs each morning.
- You will use 2 pouches of ESTRASORB each morning: 1 pouch for the right leg and 1 pouch for the left leg.
- Apply 1 ESTRASORB pouch of medicine to the left thigh and calf then apply 1 ESTRASORB pouch of medicine to the right thigh and calf.
- **Do not** apply sunscreen at the same time you apply ESTRASORB. Sunscreen may affect the way ESTRASORB works and cause you to get too much ESTRASORB.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about whether you still need treatment with ESTRASORB.

What are the possible side effects of ESTRASORB?

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:

- heart attack
- stroke
- blood clots
- breast cancer

- cancer of the lining of the uterus (womb)
- cancer of the ovary
- dementia
- gallbladder disease
- high or low blood calcium
- changes in vision
- high blood pressure
- high levels of fat (triglyceride) in your blood
- liver problems
- changes in your thyroid hormone levels
- swelling or fluid retention
- cancer changes in endometriosis
- enlargement of benign tumors of the uterus (“fibroids”)
- worsening swelling of face or tongue (angioedema) in women with a history of angioedema
- changes in laboratory test results such as bleeding time and high blood sugar levels

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- new breast lumps
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue

Common side effects of ESTRASORB include:

- headache
- breast pain
- irregular vaginal bleeding or spotting
- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection

Tell your healthcare provider if you have side effects that bother you or do not go away. These are not all of the possible side effects of ESTRASORB. Call your doctor for medical advice about side effects. You may report side effects to Exeltis USA, Inc. at 1-877-324-9349, or to FDA at 1-800-FDA-1088.

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

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

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

- 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 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 healthcare provider for ways to lower your chances of getting heart disease.

How should I store ESTRASORB?

- Store ESTRASORB at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ESTRASORB and all other medicines out of the reach of children.

General information about safe and effective use of ESTRASORB

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflets. Do not use ESTRASORB for a condition for which it was not prescribed. Do not give ESTRASORB to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about ESTRASORB that is written for health professionals.

For more information call 1-877-324-9349.

What are the ingredients in ESTRASORB?

Active ingredient: estradiol.

Inactive ingredients: soy bean oil, water, polysorbate 80, and ethanol.

INSTRUCTIONS FOR USE
ESTRASORB (es-truh-sawrb)
(estradiol topical emulsion)

Read these Instructions for Use before you start using ESTRASORB and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

To apply ESTRASORB you will need 2 pouches of ESTRASORB, 1 pouch for each leg: See Figure A



Note:

Figure A

- ESTRASORB should be applied to clean, dry skin of both legs each morning.
- Every morning you will apply 2 pouches of ESTRASORB.
- You should only open 1 ESTRASORB pouch at a time.

Step 1. Open 1 ESTRASORB pouch.

- Cut or tear the ESTRASORB pouch at the notches indicated at the top of the pouch. See **Figure B**.

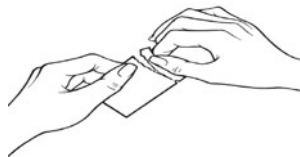


Figure B Step

2. Apply ESTRASORB to your left thigh.

- Apply ESTRASORB to the top of your left thigh, being careful to remove all the medicine by pushing the cream (emulsion) from the bottom of the pouch, up through the opening of the pouch. See **Figure C**.



**Figure
C**

Step 3. Rub ESTRASORB into the skin of your left leg.

- Using 1 hand or 2 hands, rub ESTRASORB into the skin of your entire left thigh and calf (lower back leg) until it is completely rubbed into your skin. **See Figures D and E.**



Figure D



Figure E

Step 4. Open the second ESTRASORB pouch.

- Cut or tear the second ESTRASORB pouch at the notches indicated near the top of the pouch. **See Figure B.**

Step 5. Apply ESTRASORB to your right thigh.

- Apply ESTRASORB to the top of your right thigh, being careful to remove all of the medicine by pushing the cream (emulsion) from the bottom of the pouch through the opening of the pouch. **See Figure F.**



**Figure
F**

Step 6. Rub ESTRASORB into the skin of your right leg.

- Using 1 hand or 2 hands, rub ESTRASORB into the skin of your entire right thigh and right calf (lower back leg) until it is completely rubbed into your skin. **See Figures G and H.**



Figure G



Figure H

Step 7. Allow the application areas to dry completely before covering with clothing to avoid transfer to other individuals.

Step 8. Wash your hands.

- After you finish applying ESTRASORB to both of your legs, be sure to wash hands well with soap and water to remove any remaining ESTRASORB. **See Figure I.**

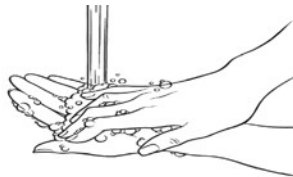


Figure I

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured for:

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Revised 9/2024