

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ENJUVIA® (synthetic conjugated estrogens, B) Tablets, for oral use
Initial U.S. Approval: 2004

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)
- Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia (5.1, 5.3)
- 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)

Estrogen Plus Progestin Therapy

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

RECENT MAJOR CHANGES

Warnings and Precautions, Malignant Neoplasms (5.2) 11/2023

INDICATIONS AND USAGE

ENJUVIA (synthetic conjugated estrogens, B) is a mixture of estrogens indicated for:

- Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause (1.1).
- Treatment of Moderate to Severe Vaginal Dryness and Pain with Intercourse, Symptoms of Vulvar and Vaginal Atrophy, due to menopause (1.2).

Limitation of Use

When prescribing solely for the treatment of moderate to severe vaginal dryness and pain with intercourse, first consider the use of topical vaginal products.

DOSAGE AND ADMINISTRATION

- Start therapy with ENJUVIA 0.3 mg once daily for the treatment of moderate to severe vasomotor symptoms associated with menopause. Dosage adjustment should be guided by the clinical response (2.1).
- Start therapy with ENJUVIA 0.3 mg once daily for the treatment of moderate to severe vaginal dryness and pain with intercourse, symptoms of vulvar and vaginal atrophy, associated with menopause (2.2).

DOSAGE FORMS AND STRENGTHS

Tablet: 0.3 mg/day, 0.45 mg/day, 0.625 mg/day, 0.9 mg/day, and 1.25 mg/day

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4, 5.2)
- Breast cancer or a history of breast cancer (4, 5.2)
- Estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema or hypersensitivity to ENJUVIA
- 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 estrogen 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 replacement therapy (5.11, 5.18)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) with ENJUVIA are: abdominal pain, headache, pain, nausea, and breast pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aspen Pharma USA Inc at +1-201-406-7955 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inducers and/or inhibitors of cytochrome CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration (7)

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

Revised: 11/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 progestin 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

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 (14.3, 14.4)*].

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 (14.3)*].

The WHI 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 (5.3)*, *Use in Specific Populations (8.5)*, and *Clinical Studies (14.4)*].

Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of 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 progestins 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

Do not use estrogen plus progestin therapy for the prevention of cardiovascular disease or dementia [see *Warnings and Precautions (5.1, 5.3)*, and *Clinical Studies (14.3, 14.4)*].

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), 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 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 (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.4)*].

Breast Cancer

The WHI estrogen plus progestin substudy also 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 MPA doses, other routes of administration, or other estrogen plus progestin 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 plus progestin therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestins 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

1.2 Treatment of Moderate to Severe Vaginal Dryness and Pain with Intercourse, Symptoms of Vulvar and Vaginal Atrophy, due to Menopause

Limitation of Use:

When prescribing solely for the treatment of moderate to severe vaginal dryness and pain with intercourse, first consider the use of topical vaginal products.

2 DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, consider addition of a progestin to reduce the risk of endometrial cancer [*see Boxed Warning*].

Generally, a woman without a uterus does not need to take a progestin in addition to her estrogen therapy. In some cases, however, hysterectomized women who have a history of endometriosis may need a progestin [see *Warnings and Precautions (5.2, 5.14)*].

Use estrogen-alone, or in combination with a progestin, at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Reevaluate 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

Start therapy with ENJUVIA 0.3 mg once daily. Make dosage adjustments based on the clinical response. Reevaluate postmenopausal women periodically as clinically appropriate to determine if treatment is still necessary.

2.2 Treatment of Moderate to Severe Vaginal Dryness and Pain with Intercourse, Symptoms of Vulvar and Vaginal Atrophy, due to Menopause

Start therapy with ENJUVIA 0.3 mg once daily.

Limitation of Use

When prescribing solely for the treatment of moderate to severe vaginal dryness and pain during intercourse, first consider the use of topical vaginal products.

3 DOSAGE FORMS AND STRENGTHS

ENJUVIA is available as tablets in 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg strengths.

4 CONTRAINDICATIONS

ENJUVIA 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 a history of these conditions [see *Warnings and Precautions (5.1)*].
- Active or recent arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions [see *Warnings and Precautions (5.1)*].
- Known anaphylactic reaction or angioedema or hypersensitivity to ENJUVIA.
- 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 risk of stroke and DVT are reported with estrogen-alone therapy. Increased risk of PE, DVT, stroke, and MI are reported with estrogen plus progestin therapy. Immediately discontinue estrogen with or without progestin therapy if any of these occur or is 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 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 (14.3)*]. 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 woman-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 daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) [see *Clinical Studies (14.3)*]. The increase in risk was demonstrated after the first year and persisted.¹ Immediately discontinue estrogen plus progestin 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 non-fatal MI, silent MI, or CHD death) in women receiving estrogen-alone compared to placebo² [see *Clinical Studies (14.3)*].

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 daily 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 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 (14.3)*].

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 (0.625 mg) plus MPA (2.5 mg) 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 (14.3)*]. 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 was reported in women receiving 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 (14.3)*]. Immediately discontinue estrogen plus progestin 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 a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times 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 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. 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 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 progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The WHI substudy of daily CE (0.625 mg)-alone provided information about breast cancer in estrogen-alone users. 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) compared to placebo⁵ [see *Clinical Studies (14.3)*].

After a mean follow-up of 5.6 years, the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg) reported an increased risk of invasive breast cancer in women who took daily CE plus MPA compared to placebo. 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 [see *Clinical Studies (14.3)*]. 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 (14.3)*].

Consistent with the WHI clinical trials, 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 generally 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 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 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 CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24) but 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 exposure (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 (14.4)*].

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 four 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 (14.4)*].

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 (14.4)*].

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 ENJUVIA, 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 ENJUVIA pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Discontinue estrogens, including ENJUVIA, if examination reveals papilledema or retinal vascular lesions.

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

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

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

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 preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of ENJUVIA 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 ENJUVIA.

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 ENJUVIA 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 a cardiac or renal impairment. Discontinue estrogen-alone therapy 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 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 a progestin 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 outweigh the risks in such women.

5.16 Exacerbation of Other Conditions

Estrogen therapy, including ENJUVIA, 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 such women.

5.17 Laboratory Tests

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

5.18 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 anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
- Increased thyroid-binding globulin (TBG) 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], 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 HDL₂ cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, and increased triglyceride levels.
- Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders [see *Boxed Warnings, Warnings and Precautions (5.1)*]
- Malignant Neoplasms [see *Boxed Warnings, 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.

In a 12-week clinical trial, 209 postmenopausal women with vasomotor symptoms were treated with ENJUVIA. Adverse reactions that occurred in the study at a rate greater than or equal to 3% and greater than placebo are summarized in [Table 1](#).

Table 1: Number (%) of Women Reporting Adverse Reactions with ≥3 Percent Occurrence Rate and Greater than Placebo by Body System and Treatment Group

Body System/Adverse Reaction	0.3 mg n=68	0.625 mg n=72	1.25 mg n=69	Placebo n=72
Number of Patients in Safety Sample (%)	68 (100)	72 (100)	69 (100)	72 (100)
Number of Patients with Adverse Reactions (%)	49 (72)	55 (76)	56 (81)	51 (71)
Number of Patients without Adverse Reactions (%)	19 (28)	17 (24)	13 (19)	21 (29)
Body as a Whole				
Abdominal Pain	3 (4)	11 (15)	3 (4)	7 (10)
Accidental Injury	6 (9)	2 (3)	3 (4)	5 (7)
Asthenia	2 (3)	3 (4)	2 (3)	0

Body System/Adverse Reaction	0.3 mg n=68	0.625 mg n=72	1.25 mg n=69	Placebo n=72
Chest Pain	2 (3)	3 (4)	0	0
Chills	0	3 (4)	1 (1)	1 (1)
Flu Syndrome	4 (6)	3 (4)	5 (7)	3 (4)
Headache	10 (15)	18 (25)	11 (16)	15 (21)
Pain	10 (15)	14 (19)	7 (10)	6 (8)
Digestive System				
Constipation	3 (4)	2 (3)	1 (1)	2 (3)
Diarrhea	4 (6)	2 (3)	3 (4)	4 (6)
Flatulence	3 (4)	5 (7)	3 (4)	2 (3)
Nausea	5 (7)	7 (10)	8 (12)	6 (8)
Metabolic and Nutritional Disorders				
Peripheral Edema	1 (2)	3 (4)	3 (4)	2 (3)
Nervous System				
Depression	2 (3)	3 (4)	1 (1)	1 (1)
Dizziness	5 (7)	3 (4)	1 (1)	3 (4)
Emotional Lability	2 (3)	3 (4)	1 (1)	1 (1)
Paresthesia	0	4 (6)	1 (1)	0
Respiratory System				
Bronchitis	0	3 (4)	5 (7)	3 (4)
Cough Increased	1 (2)	2 (3)	3 (4)	2 (3)
Pharyngitis	3 (4)	2 (3)	0	0
Rhinitis	3 (4)	4 (6)	5 (7)	4 (6)
Sinusitis	2 (3)	3 (4)	5 (7)	2 (3)
Skin and Appendages				
Acne	0	3 (4)	1 (1)	0
Fungal Dermatitis	1 (2)	0	3 (4)	1 (1)
Pruritus	2 (3)	2 (3)	4 (6)	3 (4)
Urogenital System				
Breast Pain	0	9 (13)	10 (15)	3 (4)
Dysmenorrhea	1 (2)	6 (8)	1 (1)	2 (3)
Vaginitis	1 (2)	5 (7)	2 (3)	3 (4)

In a second 12-week clinical trial, 310 women with symptoms of vulvar and vaginal atrophy were treated (154 women with ENJUVIA 0.3 mg tablets and 156 women with placebo). Adverse reactions that occurred in the study at a rate greater than or equal to 3% and greater than placebo are summarized in *Table 2*.

Table 2: Number (%) of Women Reporting Adverse Reactions with ≥ 3 Percent Occurrence Rate and Greater than Placebo by Body System and Treatment Group

Body System/Adverse Reaction	0.3 mg n=154	Placebo n=156
Number of Patients in Safety Sample (%)	154 (100)	156 (100)
Number of Patients with Adverse Reactions (%)	83 (54)	74 (47)
Number of Patients without Adverse Reactions (%)	71 (46)	82 (53)
Infections and Infestations		
Upper Respiratory Tract Infection	6 (4)	4 (3)
Sinusitis	5 (3)	2 (1)
Reproductive System and Breast Disorders		
Breast Tenderness	6 (4)	1 (1)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	6 (4)	2 (1)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ENJUVIA. 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.

Gastrointestinal Disorders: abdominal discomfort, abdominal distension, nausea

Immune System Disorders: anaphylactic reaction, hypersensitivity

Musculoskeletal and connective tissue disorders: muscle spasms

Nervous System Disorders: headache, dizziness

Psychiatric disorders: insomnia

Reproductive system and Breast Disorders: breast pain, breast tenderness

Skin and Subcutaneous Tissue Disorders: alopecia, rash, urticaria

Vascular Disorders: deep vein thrombosis, thrombosis

7 DRUG INTERACTIONS

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

ENJUVIA is not indicated for use in pregnancy. There are no data with the use of ENJUVIA 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 (estrogen and progestin) 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 breast-feeding should be considered along with the mother's clinical need for ENJUVIA and any potential adverse effects on the breast-fed child from ENJUVIA or from the underlying maternal condition.

8.4 Pediatric Use

Risk Summary

ENJUVIA is not indicated 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 studies utilizing ENJUVIA to determine whether those over 65 years of age differ from younger subjects in their response to ENJUVIA.

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 (14.3)*].

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 (14.3)*].

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 (14.4)*].

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 (14.4)*].

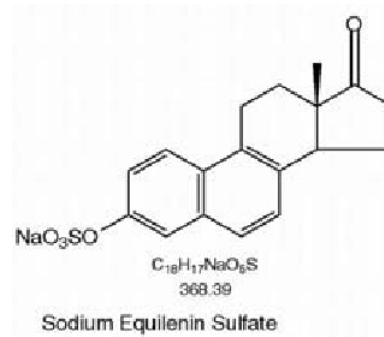
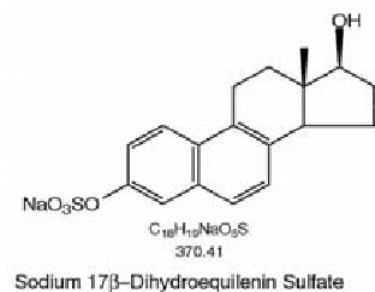
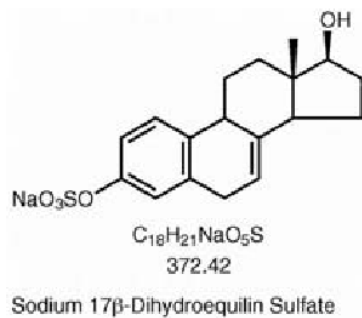
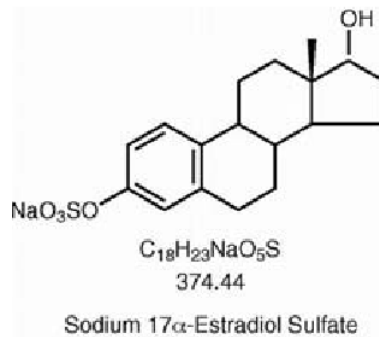
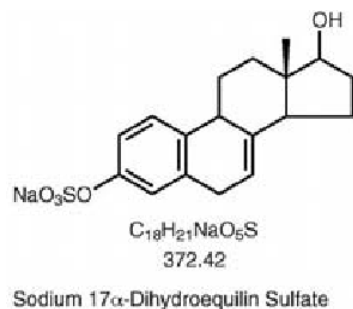
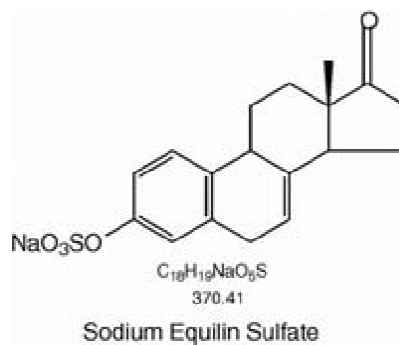
10 OVERDOSAGE

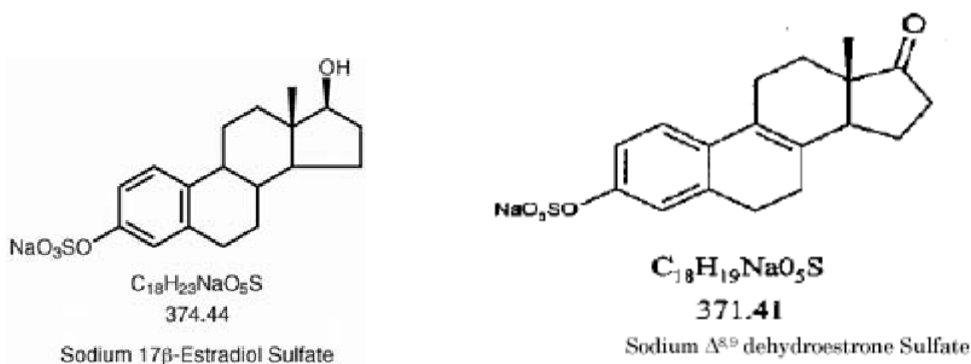
Overdosage of estrogen may cause nausea and vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of ENJUVIA therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

ENJUVIA (synthetic conjugated estrogens, B) tablets contain a blend of ten (10) 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 β -dihydroequilin sulfate, sodium 17 α -dihydroequilenin sulfate, sodium 17 β -dihydroequilenin sulfate, sodium equilenin sulfate, sodium 17 β -estradiol sulfate, and sodium $\Delta^{8,9}$ -dehydroestrone sulfate.

The structural formulae for these estrogens are:





ENJUVIA tablets for oral administration are available in 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg strengths of synthetic conjugated estrogens, B. These tablets contain the following inactive ingredients: ascorbyl palmitate, butylated hydroxyanisole, colloidal silicon dioxide, edetate disodium dehydrate, plasticized ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, purified water, iron oxide red, titanium dioxide, polyethylene glycol, polysorbate 80, triacetate and triacetin/glycerol. In addition, the 0.45 mg tablets contain iron oxide black and iron oxide yellow; the 0.9 mg tablets also contain D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, and FD&C yellow no. 6 aluminum lake; and the 1.25 mg tablets contain iron oxide yellow.

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 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 FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones in postmenopausal women.

12.2 Pharmacodynamics

Generally, a serum estrogen concentration does not predict an individual woman's therapeutic response to ENJUVIA 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

Synthetic conjugated estrogens, B are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. ENJUVIA tablets release synthetic conjugated estrogens, B slowly over a period of several hours. *Table 3* and *Table 4* summarize the mean pharmacokinetic parameters for unconjugated (free) and conjugated (total) estrogens following single administration of two 0.625 mg tablets to 21 healthy postmenopausal women under fasting conditions. The effect of food on the bioavailability of synthetic conjugated estrogens, B following administration of ENJUVIA tablets has not been studied. However, the presence of food did not significantly affect the pharmacokinetics of a similar formulation of synthetic conjugated estrogens, B.

Table 3: Mean Pharmacokinetic Parameters of Unconjugated (Free) Estrogens Following a Single Dose of 2 x 0.625 mg ENJUVIA Tablets Under Fasting Conditions*

	C_{max} (pg/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	AUC _{0-48h} (pg•hr/mL)
Baseline-corrected estrone (% CV)	75.87 (39)	9.29 (25)	23.46 (59)	1601.59 (41)
Equilin (% CV)	41.94 (49)	8.38 (27)	15.09 (55)	707.21 (46)

C_{max} = peak plasma concentration; t_{max} = time peak concentration occurs; $t_{1/2}$ = apparent terminal-phase disposition half-life; AUC_{0-48h} = total area under the concentration-time curve from time zero to time of last quantifiable concentration (48h); * $\Delta^{8,9}$ Dehydroestrone (free) levels were below the assay limit of quantitation; CV= Coefficient of Variance

Table 4: Mean Pharmacokinetic Parameters of Conjugated (Total) Estrogens Following a Single Dose of 2 x 0.625 mg ENJUVIA Tablets Under Fasting Conditions

	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC _{0-48h} (ng•h/mL)
Baseline-corrected estrone (% CV)	3.74 (29)	8.00 (27)	14.26 (26)	62.03 (34)
Equilin (% CV)	3.69 (44)	8.05 (36)	11.28 (28)	58.25 (53)
$\Delta^{8,9}$ Dehydroestrone (% CV)	0.74 (32)	7.55 (37)	14.14 (26)	12.93 (39)

C_{max} = peak plasma concentration; t_{max} = time peak concentration occurs; $t_{1/2}$ = apparent terminal-phase disposition half-life; AUC_{0-48h} = total area under the concentration-time curve from time zero to time of last quantifiable concentration (48h); CV= Coefficient of Variance

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 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 intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant portion 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

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The mean (SD) apparent terminal elimination half-life ($t_{1/2}$) of conjugated estrone is 14 (\pm 6) hours and conjugated equilin is 11 (\pm 6) hours.

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

A randomized, double-blind, placebo-controlled, dose-ranging, multi-center clinical study was conducted to evaluate the safety and effectiveness of ENJUVIA tablets for the treatment of vasomotor symptoms in 281 naturally or surgically postmenopausal women aged 26 to 65 years who were experiencing a minimum of seven moderate to severe hot flashes per day or 50 per week at randomization. The majority (81%) of women were Caucasian (n=228) and 17.4% were Black (n=49). Women were randomized to receive ENJUVIA tablets 0.3 mg, 0.625 mg, 1.25 mg, or placebo once daily for 12 weeks.

ENJUVIA (0.3 mg, 0.625 mg, and 1.25 mg tablets) 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 ([Table 5](#) and [Table 6](#)).

Table 5: Mean Number and Mean Change in Number of Moderate to Severe Hot Flushes Per Week, ITT Population With LOCF

	0.3 mg n=66	0.625 mg n=71	1.25 mg n=69	Placebo n=70
Baseline				
Mean (SD)	104.3 (57.7)	97.3 (82.1)	86.8 (42.1)	96.4 (58.2)
Week 4				
Mean (SD)	47.0 (52.9)	23.3 (26.9)	24.6 (47.0)	57.8 (47.5)
Mean Change from Baseline (SE)	-49.8 (5.2)	-72.8 (5.0)	-68.3 (5.1)	-37.2 (5.0)
p-value versus placebo	0.005	<0.001	<0.001	---
Week 12				
Mean (SD)	30.7 (47.7)	12.2 (18.7)	12.4 (26.3)	47.5 (49.8)
Mean Change from Baseline (SE)	-66.3 (4.6)	-84.6 (4.4)	-82.6 (4.5)	-48.3 (4.5)
p-value versus placebo	<0.001	<0.001	<0.001	---

ITT= Intent to treat; LOCF= Last Observation Carried Forward, SD= Standard Deviation; SE= Standard Error

Table 6: Mean Change in Severity of Moderate to Severe Hot Flushes Per Week, ITT Population with LOCF

	0.3 mg n=66	0.625 mg n=71	1.25 mg n=69	Placebo n=70
Baseline				
Mean (SD)	2.5 (0.3)	2.5 (0.3)	2.5 (0.3)	2.5 (0.3)
Week 4				
Mean (SD)	2.1 (0.8)	1.9 (1.0)	1.5 (1.1)	2.2 (0.8)
Mean Change from Baseline (SE)	-0.5 (0.1)	-0.6 (0.1)	-1.0 (0.1)	-0.3 (0.1)
p-value versus placebo	0.036	0.002	<0.001	---
Week 12				
Mean (SD)	1.5 (1.2)	1.1 (1.2)	1.0 (1.1)	1.9 (1.1)
Mean Change from Baseline (SE)	-1.0 (0.1)	-1.4 (0.1)	-1.5 (0.1)	-0.6 (0.1)
p-value versus placebo	0.023	<0.001	<0.001	---

ITT= Intent to treat; LOCF= Last Observation Carried Forward, SD= Standard Deviation; SE= Standard Error

14.2 Effects on Vulvar and Vaginal Atrophy in Postmenopausal Women

A randomized, double-blind, placebo-controlled, multi-center clinical study was conducted to evaluate the safety and effectiveness of ENJUVIA 0.3 mg tablets for the treatment of symptoms of vulvar and vaginal atrophy in 248 naturally or surgically postmenopausal women between 32 to 81 years of age (mean 58.6 years) 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. The majority (82%) of the women were Caucasian (n=203), 11% were Hispanic (n=26), 4% were Black (n=9), and 3% were Asian (n=6). All patients were assessed for improvement in the mean change from baseline to Week 12 for three co-primary efficacy variables: most bothersome symptom of vulvar and vaginal atrophy (defined as the 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; and vaginal pH.

In this study, a statistically significant mean change between baseline and Week 12 for the group treated with ENJUVIA 0.3 mg tablets compared to placebo was observed for the symptoms, vaginal dryness and pain with intercourse. See [Table 7](#). ENJUVIA 0.3 mg tablets increased superficial cells by a mean of 17.1% as compared to 2.0% for placebo (statistically significant). A corresponding statistically significant mean reduction from baseline in parabasal cells (41.7% for ENJUVIA 0.3 mg tablets and 6.8% for placebo) was observed at Week 12. The mean reduction between baseline and Week 12 in the pH was 1.69 in the ENJUVIA 0.3 mg tablets group and 0.45 in the placebo group (statistically significant).

Table 7: Change from Baseline to Week 12 in the Severity of Vaginal Dryness and Pain with Intercourse, Symptoms That Were Identified by the Menopausal Woman as Her Most Bothersome Symptom of Vulvar and Vaginal Atrophy at Baseline

Most Bothersome Symptom at Baseline*	ENJUVIA 0.3 mg	Placebo
Vaginal Dryness		
n	56	54
Baseline Severity	2.52	2.54
Mean Severity at Week 12	0.80	1.81
Mean Change in Severity from Baseline (s.d.)	-1.71 (0.85)	-0.72 (0.66)
p-value versus placebo	<0.001	---
Pain With Intercourse		
n	35	40
Baseline Severity	2.74	2.70
Mean Severity at Week 12	0.94	1.95
Mean Change in Severity from Baseline (s.d.)	-1.80 (1.02)	-0.75 (0.95)
p-value versus placebo	<0.001	---

* Treatment differences assessed by ANCOVA or rank ANCOVA (% cell data) with baseline as covariate for the modified intent-to-treat population, last-observation-carried-forward data set.

14.3 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 either the use 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 causes. 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 8](#).

Table 8: 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
<i>Nonfatal MI^c</i>	<i>0.91 (0.73-1.14)</i>	<i>40</i>	<i>43</i>
<i>CHD death^c</i>	<i>1.01(0.71-1.43)</i>	<i>16</i>	<i>16</i>
All strokes ^c	1.33 (1.05-1.68)	45	33
<i>Ischemic stroke^c</i>	<i>1.55 (1.19-2.01)</i>	<i>38</i>	<i>25</i>
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

Event	Relative Risk CE vs. Placebo (95% nCI ^b)	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
Global index ^g	1.02 (0.91-1.13)	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, 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 fractures.⁹ The absolute excess risk of events included in the “global index” was a nonsignificant 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 with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow up of 7.1 years (see [Table 8](#)).

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 examined¹⁰ (see [Table 8](#)).

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 nonsignificant 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 reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA 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 9](#). These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 9: 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>	1.28 (1.00-1.63)	31	25
<i>CHD death</i>	1.10 (0.70-1.75)	8	8
All strokes	1.31 (1.03-1.68)	33	25
<i>Ischemic stroke</i>	1.44 (1.09-1.90)	26	18
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, 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 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]).

14.4 Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy postmenopausal women 65 to 79 years of age (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 with 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 woman-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 both 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 4,532 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 with 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 woman-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)*].

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ENJUVIA (synthetic conjugated estrogens, B) Tablets

- 0.3 mg:
The tablets are oval, white, film-coated, and debossed with “E” on one side and “1” on the reverse and are available in bottles of:
100 Tablets NDC 51285-406-02
- 0.45 mg:
The tablets are oval, mauve, film-coated, and debossed with “E” on one side and “2” on the reverse and are available in bottles of:
100 Tablets NDC 51285-407-02
- 0.625 mg:
The tablets are oval, pink, film-coated, and debossed with “E” on one side and “3” on the reverse and are available in bottles of:
100 Tablets NDC 51285-408-02

- 0.9 mg:
The tablets are oval, light blue-green, film-coated, and debossed with “E” on one side and “5” on the reverse and are available in bottles of:
100 Tablets NDC 51285-409-02
- 1.25 mg:
The tablets are oval, yellow, film-coated, and debossed with “E” on one side and “4” on the reverse and are available in bottles of:
100 Tablets NDC 51285-410-02

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions are permitted to 15° to 30°C (59 to 86°F) [See USP Controlled Room Temperature].

Keep this and all drugs out of the reach of children.

Dispense in a tight container with a child-resistant closure.

Pharmacist: Include one “Patient Information” leaflet with each prescription.

17 PATIENT COUNSELING INFORMATION

Advise women to read the FDA-approved patient labeling (Patient Information)

Vaginal Bleeding

Inform postmenopausal women to report any vaginal bleeding to their healthcare provider 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 with Estrogen-Alone Therapy

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

Manufactured By:

Teva Women’s Health, Inc.
Subsidiary of Teva Pharmaceuticals USA, Inc.
5040 Duramed Drive, Cincinnati, OH 45213

For: Aspen Global Incorporated

GBS Plaza, Cnr LaSalette & Royal Roads

Grand Bay, Mauritius

PATIENT INFORMATION

ENJUVIA® (en joo vĕ- ə)

(synthetic conjugated estrogens, B) Tablets

Read this Patient Information before you start using ENJUVIA, 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 medical condition or your treatment.

What is the most important information I should know about ENJUVIA (an estrogen mixture)?

- 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 ENJUVIA. 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 in 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 or older.
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes, or dementia.
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or 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 progestin 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 been studied in the same way, it is not known how the use of ENJUVIA will affect your chances of these conditions. You and your healthcare provider should talk regularly about whether you still need treatment with ENJUVIA.

What is ENJUVIA?

ENJUVIA is a prescription medicine that contains a mixture of estrogen hormones.

What is ENJUVIA used for?

ENJUVIA is used after menopause to:

- Reduce moderate or 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 episodes 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.

- Treat moderate to severe vaginal dryness and pain with sex, due to menopause
You and your healthcare provider should talk regularly about whether you still need treatment with ENJUVIA to control these problems. If you use ENJUVIA only to treat your vaginal dryness, or pain with sex, talk with your healthcare provider about whether a topical vaginal product would be better for you.

Who should not use ENJUVIA?

Do not start ENJUVIA 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 cancers, 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 ENJUVIA.
- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**

- **are allergic to ENJUVIA or any of its ingredients**
See the list of ingredients in ENJUVIA at the end of this leaflet.

Before you use ENJUVIA, 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 vaginal bleeding to find out the cause.
- **have any other medical conditions that may become worse while you are using ENJUVIA**

Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), diabetes, epilepsy (seizures), migraine, endometriosis, lupus, angioedema (swelling of the face and tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

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

ENJUVIA is not for pregnant women.

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

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

- **are breastfeeding**

The hormones in ENJUVIA can pass into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how ENJUVIA works. ENJUVIA may also 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 ENJUVIA?

- Use ENJUVIA exactly as your healthcare provider tells you to use it.
- Take one ENJUVIA tablet by mouth at the same time each day.
- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.
- You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are using and whether you still need treatment with ENJUVIA.
- ENJUVIA may be taken with or without food.

What are the possible side effects of ENJUVIA?

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
- cancer of the lining of the uterus (womb)
- breast cancer
- cancer of the ovary
- dementia
- gallbladder disease
- high or low blood calcium
- visual abnormalities
- high blood pressure
- high levels of fat (triglycerides) in your blood
- liver problems
- changes in your thyroid hormone levels
- fluid retention

- cancer changes of endometriosis
- enlargement of benign tumors of the uterus (“fibroids”)
- worsening swelling of face and tongue (angioedema) in women who have a history of angioedema

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 ENJUVIA include:

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

These are not all the possible side effects of ENJUVIA. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effects that bother you or does not go away.

You may report side effects to Aspen Pharma USA Inc at +1-201-406-7955 or to FDA at 1-800-FDA-1088.

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

- Talk with your healthcare provider regularly about whether you should continue using ENJUVIA.
- 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 a woman 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 ENJUVIA.
- 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 a higher chance of getting heart disease.

Ask your healthcare provider for ways to lower your chance of getting heart disease.

How should I store ENJUVIA?

- Store ENJUVIA at room temperature between 59°F to 86°F (15°C to 30°C).

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

General information about safe and effective use of ENJUVIA.

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

This leaflet provides a summary of the most important information about ENJUVIA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ENJUVIA that is written for healthcare professionals.

You may also obtain further information by calling the toll-free number 1-201-406-7955.

What are the ingredients in ENJUVIA?

Active Ingredient: synthetic conjugated estrogens, B.

Inactive Ingredients: ascorbyl palmitate, butylated hydroxyanisole, colloidal silicon dioxide, edetate disodium dehydrate, plasticized ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, purified water, iron oxide red, titanium dioxide, polyethylene glycol, polysorbate 80, triacetate and triacetin/glycerol. In addition, the

- 0.45 mg tablets contain iron oxide black and iron oxide yellow;
- 0.9 mg tablets also contain D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake and FD&C yellow no. 6 aluminum lake;
- 1.25 mg tablets contain iron oxide yellow.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured By:

Teva Women's Health, Inc.

Subsidiary of Teva Pharmaceuticals USA, Inc.

5040 Duramed Drive, Cincinnati, OH 45213

For: Aspen Global Incorporated

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