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 WITH UNOPPOSED ESTROGEN IN WOMEN WITH A UTERUS
See full prescribing information for complete boxed warning.

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)**

RECENT MAJOR CHANGES

Boxed Warning, Cardiovascular Disorders, Breast Cancer, Probable Dementia	removed 2/2026
Dosage and Administration, Important Use Information (2.1)	2/2026
Contraindications (4)	2/2026
Warnings and Precautions, Cardiovascular Disorders (5.1)	2/2026
Warnings and Precautions, Malignant Neoplasms (5.2)	2/2026
Warnings and Precautions, Risks Associated with Concomitant Use of Estrogen Plus Progestogen (5.3)	2/2026
Warnings and Precautions, Probable Dementia	removed 2/2026
Warnings and Precautions, Addition of a Progestogen When a Woman Has Not Had a Hysterectomy	removed 2/2026

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, 5.9)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

WARNINGS AND PRECAUTIONS

- Cardiovascular Disorders: Increased risks of PE, DVT, and stroke with estrogen-alone therapy. Discontinue if an arterial or venous thrombotic or thromboembolic event occurs. (5.1)
- 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, 5.8)
- Monitor thyroid function in women on thyroid replacement therapy (5.10, 5.17)

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: 2/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER WITH UNOPPOSED ESTROGEN IN WOMEN WITH A UTERUS

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestogen to estrogen-only 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 menopausal women with abnormal genital bleeding of unknown etiology *[see Warnings and Precautions (5.2)]*.**

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

2.1 Important Use Information

The timing of Enjuvia initiation can affect the overall benefit-risk profile. Consider initiating Enjuvia in women < 60 years old or < 10 years since menopause onset *[see Warnings and Precautions (5), Use in Specific Populations (8.5) and Clinical Studies (14)]*.

When estrogen is prescribed for a menopausal woman with a uterus, the addition of a progestogen has been shown to reduce the risk of endometrial cancer. There are possible risks associated with the use of progestogens plus estrogens that differ from those of estrogen-alone regimens. See prescribing information for progestogens indicated for the prevention of endometrial hyperplasia in non-hysterectomized menopausal women receiving estrogens *[see Warnings and Precautions (5.2, 5.3)]*.

Generally, a woman without a uterus does not need to use a progestogen with estrogen therapy. In some cases, however, hysterectomized women with a history of endometriosis may benefit from the addition of a progestogen *[see Warnings and Precautions (5.13)]*.

2.2 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.

2.3 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:

- Abnormal genital bleeding of unknown etiology *[see Warnings and Precautions (5.2)]*.
- Current or 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 arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions *[see Warnings and Precautions (5.1)]*.
- Known anaphylactic reaction, angioedema or hypersensitivity to ENJUVIA.
- Hepatic impairment or disease *[see Warnings and Precautions (5.9)]*.
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

Enjuvia is contraindicated in women with active DVT, PE, stroke, or a history of these conditions [*see Contraindications (4)*]. Immediately discontinue Enjuvia if a PE, DVT, or stroke, occurs or is suspected. If feasible, discontinue Enjuvia at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

The safety and efficacy of Enjuvia for the prevention of cardiovascular disorders have not been established.

The Women's Health Initiative (WHI) estrogen-alone trial reported increased risks of pulmonary embolism (PE), deep vein thrombosis (DVT), and stroke, in postmenopausal women (50 to 79 years of age, average age 63.4 years) during 7.2 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] relative to placebo. Analyses were also conducted in women aged 50-59 years, a group of women more likely to present with new onset of moderate to severe VMS compared to women of other age groups in the trial.

Only daily oral 0.625 mg CE was studied in the WHI estrogen-alone trial. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events to lower CE doses, other routes of administration, or other estrogen 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 *[see Clinical Studies (14.3)]*.

Venous Thromboembolism

In women aged 50-59 years, the WHI estrogen-alone trial reported a relative risk for PE of 1.53 (95% confidence interval [CI], 0.63, 3.75) for CE compared to placebo, with an absolute risk difference of 4 per 10,000 women-years (WYs; 10 versus 6). The relative risk for DVT was 1.66 (95% CI 0.75, 3.67) for CE compared to placebo, with a risk difference of 5 per 10,000 WYs (13 versus 8).

In the overall study population of women aged 50-79 years, the WHI estrogen-alone trial reported a relative risk of PE of 1.35 (95% CI 0.89, 2.05) for CE compared to placebo, with a risk difference of 4 per 10,000 WYs (14 versus 10). The relative risk for DVT was 1.48 (95% 1.06, 2.07) for CE compared to placebo, with a risk difference of 7 per 10,000 WYs (23 versus 15) *[see Clinical Studies (14.3)]*.

Stroke

In women aged 50-59 years, the WHI estrogen-alone trial reported a relative risk for stroke of 0.99 (95% 0.53, 1.85) for CE compared to placebo, with a risk difference of -1 per 10,000 WYs (16 versus 17).

In the overall study population of women aged 50-79 years, the WHI estrogen-alone trial reported a relative risk for stroke of 1.35 (95%, 1.07, 1.70) for CE compared to placebo, with a risk difference of 11 per 10,000 WYs (45 versus 34) *[see Clinical Studies (14.3)]*.

5.2 Malignant Neoplasms

Endometrial Cancer

In Enjuvia-treated menopausal women with a uterus with persistent or recurring abnormal genital bleeding of unknown etiology, perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to assess for 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 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 the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. 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 estrogen-alone therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. There are, however, possible risks associated with the use of progestogens plus estrogens that differ from those of estrogen-alone regimens *[see Warnings and Precautions (5.3)].*

Breast Cancer

Surveillance measures for breast cancer, such as breast examinations and mammography, are recommended. The use of estrogen-alone therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

In the WHI estrogen-alone trial, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer. Among women 50-59 years old, the relative risk was 0.82 (95% CI, 0.50, 1.34) for CE compared to placebo, with a risk difference of -5 per 10,000 WYs (24 versus 29). In the overall study population of women aged 50-79 years (average age 63.4 years), the relative risk was 0.79 (95% CI, 0.61, 1.02), with a risk difference of -7 per 10,000 WYs (28 versus 35) *[see Clinical Studies (14.3)].* However, a large meta-analysis including 24 prospective studies of postmenopausal women comparing current use of estrogen-only products with use duration of 5 to 14 years (average of 9 years) versus never use reported a relative risk for breast cancer of 1.33 (95% CI, 1.28 to 1.38).[2]

Ovarian Cancer

A large meta-analysis including 17 prospective studies of postmenopausal women compared current use of estrogen-only products versus never use and reported a relative risk for ovarian cancer of 1.37 (95% CI, 1.26 to 1.50). The duration of hormone therapy use that was associated with an increased risk of ovarian cancer is unknown.[3]

5.3 Risks Associated with Concomitant Use of Estrogen Plus Progestogen

If Enjuvia is administered with a progestogen, there are possible risks associated with the use of progestogens plus estrogens that differ from those of estrogen-alone regimens. Refer to prescribing information for progestogens indicated for the prevention of endometrial hyperplasia in non-hysterectomized menopausal women receiving estrogens.

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 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.

5.8 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.

5.9 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.

5.10 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 T_4 and T_3 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.

5.11 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

5.12 Hypocalcemia

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

5.13 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.

5.14 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.

5.15 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.

5.16 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.

5.17 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), T_4 levels (by column or by

radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. 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 HDL_2 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)

Body System/Adverse Reaction	0.3 mg n=68	0.625 mg n=72	1.25 mg n=69	Placebo n=72
Asthenia	2 (3)	3 (4)	2 (3)	0
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)

Body System/Adverse Reaction	0.3 mg n=68	0.625 mg n=72	1.25 mg n=69	Placebo n=72
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 trial (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)*].

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 probable dementia in women receiving estrogen-alone *[see Warnings and Precautions (5.3), and Clinical Studies (14.4)].*

Since the trial was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger menopausal women *[Clinical Studies (14.3)].* The safety and efficacy of Enjuvia for the prevention of dementia has not been established.

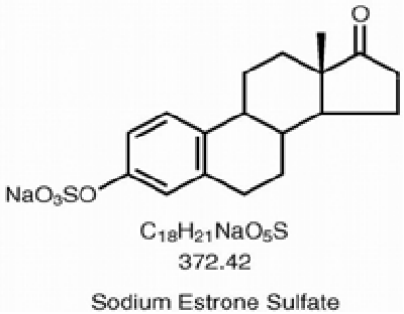
10 OVERDOSAGE

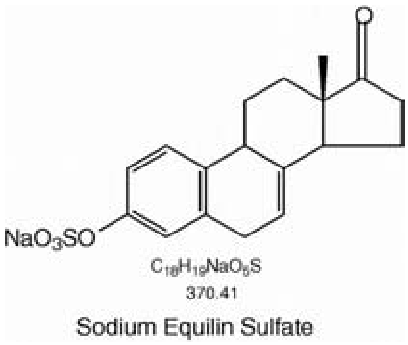
Overdosage of estrogen may cause nausea and vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of ENJUVIA therapy with institution of appropriate symptomatic care.

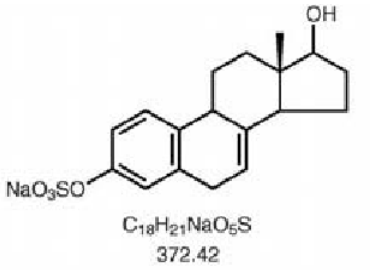
11 DESCRIPTION

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 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate, sodium 17β-estradiol sulfate, and sodium $\Delta^{8,9}$-dehydroestrone sulfate.

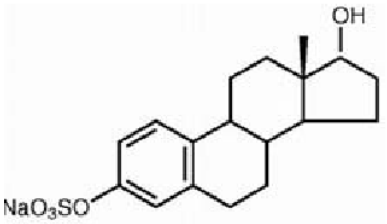
The structural formulae for these estrogens are:



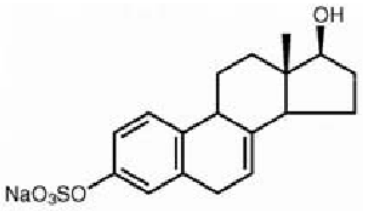




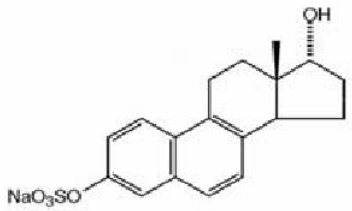
$C_{18}H_{21}NaO_5S$
372.42
Sodium 17α-Dihydroequilin Sulfate



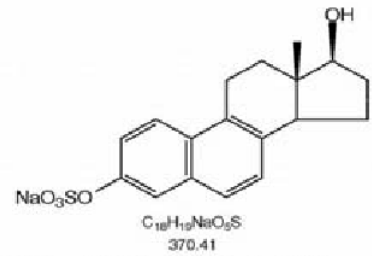
$C_{18}H_{23}NaO_5S$
374.44
Sodium 17α-Estradiol Sulfate



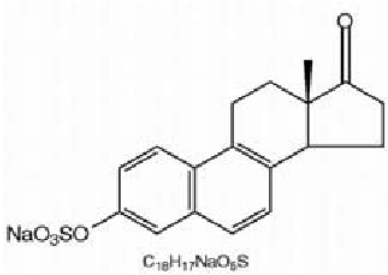
$C_{18}H_{21}NaO_5S$
372.42
Sodium 17β-Dihydroequilin Sulfate



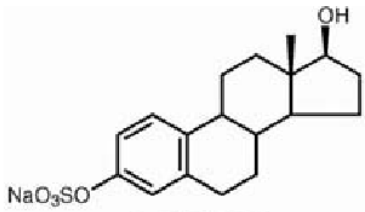
$C_{18}H_{19}NaO_5S$
370.41
Sodium 17α–Dihydroequilenin Sulfate



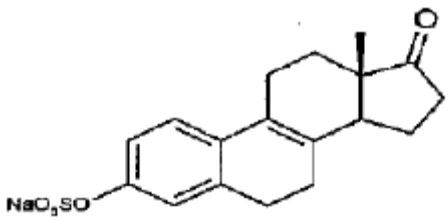
$C_{18}H_{19}NaO_5S$
370.41
Sodium 17β–Dihydroequilenin Sulfate



$C_{18}H_{17}NaO_5S$
368.39
Sodium Equilenin Sulfate



$C_{18}H_{23}NaO_5S$
374.44
Sodium 17β-Estradiol Sulfate



$C_{18}H_{19}NaO_5S$
371.41
Sodium $\Delta^{8,9}$ dehydroestrone Sulfate

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)	$t_{½}$ (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 ($t_{½}$) of conjugated estrone is 14 (± 6) hours and conjugated equilin is 11 (± 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 flushes 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)

	0.3 mg n=66	0.625 mg n=71	1.25 mg n=69	Placebo n=70
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 ≤ 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 Estrogen-Alone Trial

The WHI estrogen-alone trial enrolled predominantly healthy postmenopausal women in trial to assess the risks and benefits of daily oral CE (0.625 mg)-alone 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, colorectal cancer, hip fracture, or death due to other cause. This trial did not evaluate the effects of CE-alone on menopausal symptoms.

The WHI estrogen-alone trial 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. Centrally adjudicated results for stroke events, after an average follow- up of 7.1 years, reported estrogen-alone increased the risk for ischemic stroke compared to placebo, and this excess risk was present in all subgroups of women examined.

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 trial, after an average follow-up of 7.1 years. [4,5]

Results of the estrogen-alone trial, which included 10,739 women (average age of 63 years, range 50 to 79 years; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other), after an average follow- up of 7.1 years are presented in Table 8.

Table 8: RelativeRisk and Risk Difference Observed in the WHI Estrogen-Alone Trial at an Average of 7.1 Years of Follow-up[a]

Event	Relative Ratio (95% CI)[c]	Risk Difference (CE vs placebo/10,000 WYs)
CHD events *Non-fatal MI* *CHD death*	0.94 (0.78-1.14) *0.97 (0.79-1.21)* *1.00 (0.77-1.31)*	-3 (55 vs 58) *-1 (44 vs 45)* *0 (29 vs 29)*
All strokes	1.35 (1.07-1.70)	11 (45 vs 34)
Deep vein thrombosis[d]	1.48 (1.06– 2.07)	7 (23 vs 15)
Pulmonary embolism	1.35 (0.89-2.05)	4 (14 vs 10)
Invasive breast cancer[e]	0.79 (0.61-1.02)	-7 (28 vs 35)
Colorectal cancer	1.15 (0.81-1.64)	2 (17 vs 15)
Hip fracture	0.67 (0.46-0.96)	-6 (13 vs 19)
Vertebral fractures[d]	0.64 (0.44-0.93)	-6 (12 vs 18)
Total fractures[d]	0.72 (0.64-0.80)	-61 (153 vs 214)
Overall Mortality[c,f]	1.03 (0.88-1.21)	3 (80 vs 77)
Global Index[g]	1.03 (0.93-1.13)	4 (208 vs 204)

[a] Adapted from 2013 WHI trial (CE n=5,310, placebo n=5,429). WHI publications can be viewed at www.nhlbi.nih.gov/whi..
[b] Results are based on centrally adjudicated data.
[c] In the WHI studies, hazard ratios were estimated using Cox proportional hazards models comparing treatment to placebo; however, they are described here as relative risks. 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* 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, PE, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The study results for women 50-59 years old in the WHI estrogen-alone trial are shown in Table 9.

Table 9: Relative Risk and Risk Difference Observed Among Women 50-59 Years of Age in the WHI Estrogen – Alone Trial at an Average of 7.1 Years[a,b]

Event	Relative Ratio (95% CI)[c]	Risk Difference (CE vs placebo/10,000 WYs)
CHD events *Non-fatal MI* *CHD death*	0.60 (0.35-1.04) *0.55 (0.31-1.00)* *0.80 (0.32-2.04)*	-11 (17 vs 28) *-11 (14 vs 25)* *-1 (7 vs 8)*
All strokes	0.99 (0.53-1.85)	-1 (16 vs 17)
Deep vein thrombosis[d]	1.66 (0.75-3.67)	5 (13 vs 8)
Pulmonary embolism	1.53 (0.63-3.75)	4 (10 vs 6)
Invasive breast cancer[e]	0.82 (0.50-1.34)	-5 (24 vs 29)
Colorectal cancer	0.71 (0.30-1.67)	-3 (7 vs 10)
Hip fracture	5.01 (0.59-42.91)	3 (1 vs 3)
Vertebral fractures[d]	0.50 (0.17-1.47)	-4 (4 vs 8)
Total fractures[d]	0.90 (0.72-1.11)	-16 (133 vs 149)
Overall Mortality[c,f]	0.70 (0.46-1.09)	-11 (29 vs 40)
Global Index[g]	0.84 (0.66-1.07)	-19 (98 vs 117)

[a] Adapted from 2013 WHI trial (CE n=1,639; placebo=1,674). WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Results are based on centrally adjudicated data.
[c] In the WHI studies, hazard ratios were estimated using Cox proportional hazards models comparing treatment to placebo; however, they are described here as relative risks. 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, PE, colorectal cancer, hip fracture, or death due to other causes.

14.4 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 (45% were 65 to 69 years of age, 36% were 70 to 74 years of age, and 19% 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. 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.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95% 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. 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)]*.[6]

15 REFERENCES

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4. Anderson GL, et al; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004 Apr 14;291(14):1701-12. doi: 10.1001/jama.291.14.1701. PMID: 15082697.
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6. Espeland MA, Rapp SR, Shumaker SA, Brunner R, Manson JE, Sherwin BB, Hsia J, Margolis KL, Hogan PE, Wallace R, Dailey M, Freeman R, Hays J; Women's Health Initiative Memory Study. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004 Jun 23;291(24):2959-68. doi: 10.1001/jama.291.24.2959. PMID: 15213207.

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, LLC
Subsidiary of Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

For: **Aspen Pharma USA Inc.,**
Bedminster, NJ 07921

PATIENT INFORMATION

ENJUVIA® (en joo vē- 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 ENJUVUA (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.
- Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, 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.
- 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, LLC
Subsidiary of Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

For: **Aspen Pharma USA Inc.,**
Bedminster, NJ 07921

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