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RESEARCH**

APPLICATION NUMBER:

21-609

APPROVED LABELING

Package Insert

ENJUVIA™

(synthetic conjugated estrogens, B)

Tablets

R_x only

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

(See **WARNINGS, Malignant neoplasms, Endometrial cancer.**)

CARDIOVASCULAR AND OTHER RISKS

Estrogens and progestins should not be used for the prevention of cardiovascular disease or dementia.

(See **WARNINGS, Cardiovascular disorders and Dementia.**)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL**

PHARMACOLOGY, Clinical Studies and WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated equine estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use.**)

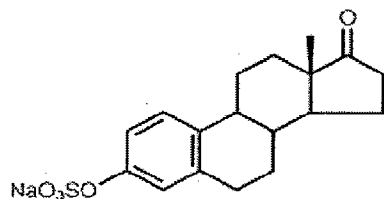
Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

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

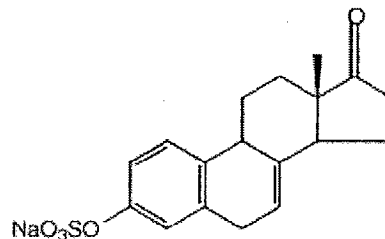
17 α -dihydroequilenin sulfate, sodium 17 β -dihydroequilenin sulfate, sodium equilenin sulfate, sodium 17 β -estradiol sulfate, and sodium $\Delta^{8,9}$ -dehydroestrone sulfate.

The structural formulae for these estrogens are:



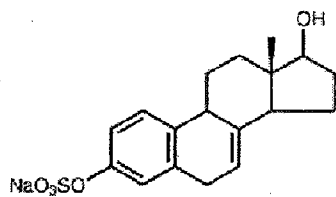
$C_{18}H_{21}NaO_5S$
372.42

Sodium Estrone Sulfate



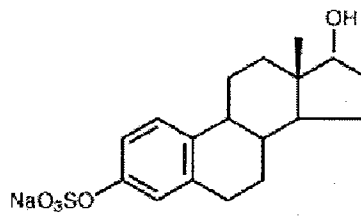
$C_{18}H_{19}NaO_5S$
370.41

Sodium Equilin Sulfate



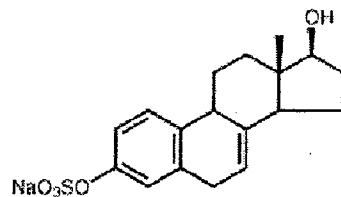
$C_{18}H_{21}NaO_5S$
372.42

Sodium 17 α -Dihydroequilin Sulfate



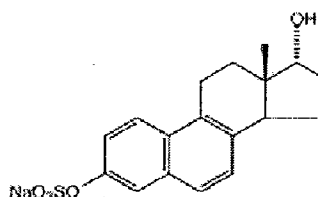
$C_{18}H_{23}NaO_5S$
374.44

Sodium 17 α -Estradiol Sulfate



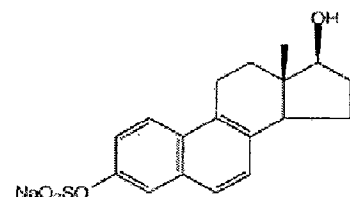
$C_{18}H_{21}NaO_5S$
372.42

Sodium 17 β -Dihydroequilin Sulfate



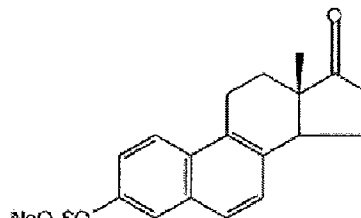
$C_{18}H_{19}NaO_5S$
370.41

Sodium 17 α -Dihydroequilenin Sulfate



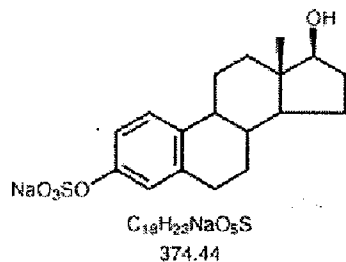
$C_{18}H_{19}NaO_5S$
370.41

Sodium 17 β -Dihydroequilenin Sulfate

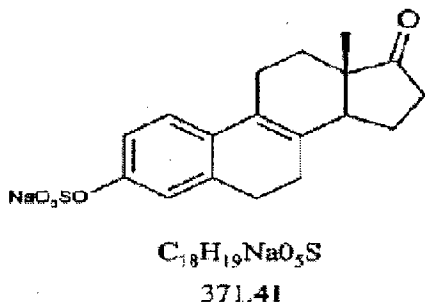


$C_{18}H_{17}NaO_5S$
368.39

Sodium Equilenin Sulfate



Sodium 17β-Estradiol Sulfate



Sodium Androsterone Sulfate

ENJUVIA tablets for oral administration are available in 0.3 mg, 0.45 mg, 0.625 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 and the 1.25 mg tablets contain iron oxide yellow.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones in postmenopausal women.

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 1 and Table 2 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 1. Mean Pharmacokinetic Parameters of Unconjugated 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 (free) (% CV)	75.87 (39)	9.29 (25)	23.46 (59)	1601.59 (41)
Equilin (free) (% 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). Dihydroestrone (free) levels were below the assay limit of quantitation; CV= Coefficient of Variance

* Δ^{8,9}

Table 2. Mean Pharmacokinetic Parameters of Conjugated 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 (total) (% CV)	3.74 (29)	8.00 (27)	14.26 (26)	62.03 (34)
Equilin (total) (% CV)	3.69 (44)	8.05 (36)	11.28 (28)	58.25 (53)
Δ ^{8,9} Dehydroestrone (total) (%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 sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut 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.

Special Populations

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

Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Clinical Studies

Effects on vasomotor symptoms

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 patients were Caucasian (n=228) and 49 patients (17.4%) were Black. Patients were randomized to receive ENJUVIA tablets 0.3 mg, 0.625 mg, 1.25 mg, or placebo once daily for 12 weeks. At the end of the 12-week treatment period, each patient with a uterus was administered oral medroxyprogesterone acetate (MPA) once daily for 14 days.

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 3 and 4).

**Table 3. 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 8				
Mean (SD)	34.8 (50.8)	13.0 (17.8)	13.8 (27.3)	49.5 (47.9)
Mean Change from Baseline (SE)	-61.8 (4.6)	-83.0 (4.4)	-80.2 (4.5)	-45.9 (4.5)
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 4. 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 8				
Mean (SD)	1.7 (1.1)	1.5 (1.1)	1.0 (1.1)	2.0 (0.9)
Mean Change from Baseline (SE)	-0.8 (0.1)	-1.0 (0.1)	-1.5 (0.1)	-0.5 (0.1)
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;

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of 0.625 mg conjugated

equine estrogens (CE) per day alone or the use of 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A “global index” included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the “global index.” Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, and 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 5 below.

Table 5. Relative and Absolute Risk Seen in the CE/MPA Substudy of WHI^a			
Event ^c	Relative Risk CE/MPA vs. Placebo at 5.2 Years (95% CI*)	Placebo n = 8102	CE/MPA n = 8506
		Absolute risk per 10,000 women-years	
CHD events	1.29 (1.02-1.63)	30	37
<i>Non-fatal MI</i>	1.32 (1.02-1.72)	23	30
<i>CHD death</i>	1.18 (0.70-1.97)	6	7
Invasive breast cancer ^b	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index ^c	1.15 (1.03-1.28)	151	170
Deep vein thrombosis ^d	2.07 (1.49-2.87)	13	26
Vertebral fractures ^d	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures ^d	0.77 (0.69-0.86)	170	131

^a adapted from JAMA, 2002; 288:321-333

^b includes metastatic and non-metastatic breast cancer with the exception of *in situ* breast cancer

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

^d not included in Global Index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the WHI “global index,” absolute excess risks per 10,000 person-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Women's Health Initiative Memory Study

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE/MPA (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use.**)

INDICATIONS AND USAGE

ENJUVIA tablets are indicated for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

CONTRAINDICATIONS

ENJUVIA tablets should not be used in individuals with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. ENJUVIA tablets should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for ENJUVIA in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS.**)

WARNINGS

See **BOXED WARNINGS.**

The use of unopposed estrogens in a woman who has a uterus is associated with an increased risk of endometrial cancer.

1. Cardiovascular disorders.

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary

embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

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

a. ***Coronary heart disease and stroke.***

In the Women's Health Initiative (WHI) study, an increase in the number of strokes has been observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs. 30 per 10,000 women-years). The increase in risk was observed in year one and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs. 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years), a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625 mg/2.5 mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty-one 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/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. ***Venous thromboembolism (VTE).***

In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

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

2. Malignant neoplasms.

a. *Endometrial cancer.*

The use of unopposed estrogens in women with uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten 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/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen doses. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. *Breast cancer.*

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

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

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy,

invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a 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.

3. **Dementia**

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n=2,229) and 21 women in the placebo group (0.9%, n=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use**.)

4. **Gallbladder disease.**

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

5. **Hypercalcemia.**

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. **Visual abnormalities**

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be discontinued.

PRECAUTIONS

A. General

1. ***Addition of a progestin when a woman has not had a hysterectomy***

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

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

2. ***Elevated blood pressure.***

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. ***Hyperlipoproteinemia***

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. ***Impaired liver function and past history of cholestatic jaundice***

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. ***Hypothyroidism***

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal range. Patients dependent on thyroid hormone therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored to maintain their free thyroid hormone levels in an acceptable range.

6. ***Fluid retention***

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

7. ***Hypocalcemia***

Estrogens should be used with caution in individuals with severe hypocalcemia.

8. ***Ovarian cancer***

The CE/MPA sub-study of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiological studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

9. ***Exacerbation of endometriosis***

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

10. *Exacerbation of other conditions*

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

B. PATIENT INFORMATION

Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe ENJUVIA tablets.

C. LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).

D. DRUG/LABORATORY TEST INTERACTIONS

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. 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. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum, (i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG)) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL₂ cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

E. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

F. PREGNANCY

ENJUVIA tablets should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

G. NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when ENJUVIA is administered to a nursing woman.

H. PEDIATRIC USE

The safety and efficacy of ENJUVIA tablets in pediatric patients has not been established.

I. GERIATRIC USE

The safety and efficacy of ENJUVIA tablets in geriatric patients has not been established.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n=3,729) were 65 to 74 while 18% (n=803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See **WARNINGS, Dementia**.)

It is unknown whether these findings apply to estrogen alone therapy.

ADVERSE REACTIONS

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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

In a 12-week clinical trial, 209 postmenopausal women were treated with ENJUVIA. Adverse events that occurred in the study at a rate greater than or equal to 5% and greater than placebo, regardless of relationship to study drug, are summarized in Table 6.

Table 6. ENJUVIA Tablets – Number (%) of Patients Reporting Adverse Events* with ≥ 5% Occurrence Rate by Body System

Body System/Adverse Events*	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 Events (%)	49 (72)	55 (76)	56 (81)	51 (71)
Number of Patients without Adverse Events (%)	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 (8)	2 (3)	3 (4)	5 (7)
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				
Flatulence	3 (4)	5 (7)	3 (4)	2 (3)
Nausea	5 (7)	7 (10)	8 (12)	6 (8)
Nervous System				
Dizziness	5 (7)	3 (4)	1 (1)	3 (4)
Paresthesia	0	4 (6)	1 (1)	0
Respiratory System				
Bronchitis	0	3 (4)	5 (7)	3 (4)
Rhinitis	3 (4)	4 (6)	5 (7)	4 (6)
Sinusitis	2 (3)	3 (4)	5 (7)	2 (3)
Urogenital System				
Breast Pain	0	9 (12)	10 (14)	3 (4)
Dysmenorrhea	1 (2)	6 (8)	1 (1)	2 (3)
Vaginitis	1 (2)	5 (7)	2 (3)	3 (4)

*Treatment-emergent adverse events, regardless of relationship to study drug

The following additional adverse reactions have been reported with estrogen and/or progestin therapy:

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

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

3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial

infarction; stroke; increase in blood pressure.

4. **Gastrointestinal**

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

5. **Skin**

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

6. **Eyes**

Retinal vascular thrombosis, intolerance to contact lenses.

7. **Central Nervous System**

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

8. **Miscellaneous**

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need a progestin. Use of estrogen, alone or in combination with a progestin, should be prescribed with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., at 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

ENJUVIA tablets are taken orally, once daily, for the treatment of moderate to severe vasomotor symptoms associated with menopause. Patients should be started at the lowest approved dose of 0.3 mg ENJUVIA daily. Subsequent dosage adjustment may be made based upon the individual patient response. This dose should be periodically reassessed by the healthcare provider.

HOW SUPPLIED

ENJUVIA™

(synthetic conjugated estrogens, B)

Tablets

- 0.3 mg tablets are available in containers of 100 (NDC 51285-406-02).
The tablets are oval, white, convex, film-coated, and debossed with “E” on one side and “1” on the reverse.

- 0.45 mg tablets are available in containers of 100 (NDC 51285-407-02).
The tablets are oval, mauve, convex, film-coated, and debossed with "E" on one side and "2" on the reverse.
- 0.625 mg tablets are available in containers of 100 (NDC 51285-408-02).
The tablets are oval, pink, convex, film-coated, and debossed with "E" on one side and "3" on the reverse.
- 1.25 mg tablets are available in containers of 100 (NDC 51285-410-02).
The tablets are oval, yellow, convex, film-coated, and debossed with "E" on one side and "4" on the reverse.

Store at 20°-25°C (68°-77°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 for each package dispensed.

Revised December 16, 2004

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PATIENT INFORMATION

(Updated June 28, 2004)

ENJUVIA™ (synthetic conjugated estrogens, B) Tablets

Read this **PATIENT INFORMATION** before you start taking ENJUVIA, and read what you get each time you refill ENJUVIA. 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 HORMONE)?

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

Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

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

Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly to determine whether you still need treatment with ENJUVIA.

What is ENJUVIA?

ENJUVIA is a medicine that contains estrogen hormones.

What is ENJUVIA used for?

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

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

Who should not take ENJUVIA?

Do not start taking ENJUVIA if you:

- **have unusual vaginal bleeding**
- **currently have or have had certain cancers**

Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take ENJUVIA.

- **had a stroke or heart attack in the past year**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **are allergic to ENJUVIA or any of its ingredients**

See the end of this leaflet for a list of ingredients in ENJUVIA.

- **think you may be pregnant**

Tell your healthcare provider:

- **if you are breastfeeding**

The hormones in ENJUVIA can pass into your milk.

- **about all of your medical problems**

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

- **about all the medicines you take**

This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how ENJUVIA works. ENJUVIA may also affect how your other medicines work.

- **if you are going to have surgery or will be on bedrest**

You may need to stop taking estrogens.

How should I take ENJUVIA?

- Take one ENJUVIA tablet by mouth at the same time each day.
- Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.
- Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about whether you still need treatment with ENJUVIA.

- ENJUVIA may be taken with or without food.

What are the possible side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other symptoms that concern you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus (“fibroids”)
- Vaginal yeast infection

These are not all the possible side effects of ENJUVIA. For more information, ask your health-care

provider or pharmacist.

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 taking 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 taking ENJUVIA.
- Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart disease.

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 take ENJUVIA for conditions for which it is not prescribed. Do not give ENJUVIA to other people, even if they have the same symptoms you have. It may harm them.

Keep ENJUVIA out of the reach of children.

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 for information about ENJUVIA that is written for healthcare professionals.

You may also obtain further information by calling the toll free number 1-XXX-XXX-XXXX.
(To be determined).

What are the ingredients in ENJUVIA?

ENJUVIA tablets for oral administration are available in 0.3 mg, 0.45 mg, 0.625 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 and the 1.25 mg tablets contain iron oxide yellow.

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