Patient Assistance Program
250 Phillips Blvd, Ste 250, Ewing, NJ 08618
1-800-425-3122 Telephone 1-800-685-2577 Fax
Hours of Operation: Monday through Friday, 8:30 AM to 5:30 PM EST

Enjuvia™ Patient Assistance Program Eligibility Requirements

A 3-month supply of Enjuvia will be provided free of charge to patients who meet program eligibility requirements:

- Patient must be a US Resident
- Patient must be 18 years of age or older
- Patient's gross annual household income must be at or below 200% HHS Poverty Guidelines*
- Patient must provide proof of gross annual household income
  - Financial documentation must be included with the Qualification Form.
  - Proof of income includes copies of both:
    - a) federal tax return (Form 1040 or 1040EZ) for prior tax year, and
    - b) all other recent documents that show income paid to patient (and/or spouse if married), such as: wage and tax statements (W-2 forms), Social Security, Pension, or Railroad Retirement statements (SSA-1099 or similar), Statements of interest, dividends, or other income (1099-INT, 1099, 1099-DIV, or other forms)
- Patient has no insurance (public or private) or third-party payer prescription drug coverage (in whole or in part), including Medicaid or Medicare Part D
  - If patient has coverage for any prescription drug (not only Enjuvia), the patient is ineligible for this program

Additional requirements:

- Program Qualification Form must be completed in its entirety by the healthcare professional caring for the patient.
- Both patient and healthcare professional must sign the Qualification Form in the appropriate section
- Patient must sign and submit the Authorization to Disclose Form
- Healthcare professional must have a current valid state license

***** Income criterion is based on Health and Human Services Poverty Guidelines. These guidelines can be revised each new year, usually around February. Website is: http://aspe.hhs.gov/poverty/index.shtml

Please see full prescribing information.

Duramed Pharmaceuticals, Inc.
Subsidiary of Barr Pharmaceuticals, Inc.
Pomona, NY 10970

Important Safety Information

Important Information: ENJUVIA is a medicine that contains estrogen hormones. It is prescribed for relief of moderate-to-severe symptoms (hot flashes and night sweats) associated with menopause.

Important health information you should know when taking estrogens like ENJUVIA:

Estrogens increase the risk for cancer of the uterus (womb). If you experience persistent or recurring vaginal bleeding while taking estrogens let your doctor know right away, as this could be a warning sign for cancer. Your doctor should check for the cause of any unusual vaginal bleeding after menopause.

Estrogens (alone, or in combination with progestins) should not be used to prevent heart disease, heart attacks, strokes or dementia.

Estrogens (alone or in combination with progestins) may increase the risk of heart attack, stroke, blood clots, breast cancer and dementia. Because of these risks, estrogens should be used at the lowest dose for the shortest time period of time. You and your doctor should talk regularly to determine whether you still need treatment with ENJUVIA.

Duramed Pharmaceuticals, Inc. reserves the right to limit enrollment of patients to the **Enjuvia Patient Assistance Program** at any time.

The program administrators reserve the right any time and without notice to modify the application form, modify or discontinue any or all of the program and the related eligibility criteria; or at any time terminate assistance provided by the program.

October 2008

Enjuvia™ Patient Assistance Program
250 Phillips Blvd, Ste 250, Ewing, NJ 08618
Phone: 1.800.425.3122 Fax: 1.800.685.2577
Qualification Form

NM

PATIENT INFORMATION (Please Print) **Patient must be a U.S. Resident**

First Name: _____ MI: _____ Last Name: _____

Address: _____ City: _____

State: _____ Zip Code: _____ Phone: _____ Date of Birth: (mm/dd/yyyy) _____

Social Security #: _____ Patient's Diagnosis (ICD.9 Code): _____

PATIENT'S INCOME:

Current gross annual household income: $ _____ Number of household members dependent on income (including patient) _____ Number of children: _____

Patient financial documentation must be included with this application. Proof of income includes copies of both: a)your federal tax return (Form 1040 or 1040EZ) for prior tax year, **and** b) All other recent documents that show income paid to you (or your spouse if married), such as: wage and tax statements (W-2 forms), Social Security, Pension, or Railroad Retirement statements (SSA-1099 or similar), Statements of interest, dividends, or other income (1099-INT, 1099, 1099-DIV, or other forms)

PATIENT'S INSURANCE AND PRESCRIPTION COVERAGE (PARTIAL OR FULL) **Check all that apply:**

☐	Medicare	☐	Medicare Advantage (MA)	☐	Includes Rx	☐ Private Foundation	☐ Includes Rx
☐	Medicaid	☐	State/Local Government	☐	Includes Rx	☐ Medicare Medigap	☐ Includes Rx
☐	Medicaid QMB	☐	Federal Program	☐	Includes Rx	☐ Private Prescription Drug Plan (PDP)	
☐	Uninsured	☐	Private Insurance / HMO	☐	Includes Rx	☐ Other:	Specify:

If Rx Coverage is Yes, name of insurance carrier: _____ If Rx Coverage is Yes, is Enjuvia covered? ☐ Yes ☐ No

PATIENT/APPLICANT DECLARATION

I understand that completing this form does not ensure that I will qualify for this program. I verify that the information provided in this qualification form is complete and accurate. I agree to notify the Enjuvia Patient Assistance Program if I obtain prescription drug coverage or if I no longer meet the income criteria. I understand that the program administrators reserve the right any time and without notice to modify the application form, modify or discontinue any or all of the program and the related eligibility criteria; or terminate assistance provided by the program at any time. No claim may be made to any third party payer for payment for product or administration of product provided under the Program.

Patient's Original Signature: _____ Date: (mm/dd/yyyy) _____

PRESCRIBER'S INFORMATION (Please Print)

First Name: _____ MI: _____ Last Name: _____

Facility: _____ Office Contact Name: _____

Street: _____ Bldg/Suite/Floor/Room: _____

City: _____ State: _____ Zip Code: _____ Phone: _____

Fax: _____ Specialty: _____ State License #: _____

E-Mail Address: _____ When you provide your e-mail address, you agree that Duramed Pharmaceuticals, Inc. and its agents may contact you about health-related materials or programs.

ENJUVIA DOSAGE (This section of the form will serve as the Enjuvia prescription) **Quantity: 1 bottle of 100 tablets**

Check dosage:

☐ **Enjuvia™ 0.3 mg tablets** ☐ **Enjuvia™ 0.45 mg tablets** ☐ **Enjuvia™ 0.625 mg tablets** ☐ **Enjuvia™ 1.25 mg tablets**

☐ QD sig – one tablet daily ☐ QHS sig – one tablet every bedtime ☐ Other: _____

PRESCRIBER ATTESTATION

I represent that the information contained in this application is complete and accurate to the best of my knowledge. To the best of my knowledge, this patient has no prescription insurance coverage for the requested medication, including Medicaid or other public programs, and the patient has insufficient financial resources to pay for the prescribed therapy. No claim may be made to any third party payer for payment of Enjuvia™ provided by this Patient Assistance Program. Enjuvia™ received for this patient may not be sold or traded, may not be returned for credit, and is not a sample. I understand that the Enjuvia™ Patient Assistance Program has the right to modify or discontinue this program and its eligibility requirements, or to terminate assistance, at any time and without prior notice. Please indicate that you agree to these terms by signing below. Your signature also confirms that there is a valid medical need for this patient's prescription for Enjuvia™.

Prescriber's Original Signature: _____ Date: (mm/dd/yyyy) _____

Duramed Pharmaceuticals, Inc. reserves the right to limit enrollment of patients to the Enjuvia™ Patient Assistance Program at any time.

ENJUVIA™ (Synthetic Conjugated Estrogens, B) TABLETS
PATIENT ASSISTANCE PROGRAM
250 Phillips Blvd, Ste 250, Ewing, NJ 08618
Phone: 1.800.425.3122 Fax: 1.800.685.2577

Patient Authorization to Disclose Protected Health Information

To the Patient: I understand that during the course of my participation in the Enjuvia™ Patient Assistance Program, that personal identifying information provided will be provided to Duramed Pharmaceuticals, Inc. its affiliated companies and subcontractors on a need to know basis for purposes of administering the program. I understand this information constitutes Protected Health Information (PHI) under the privacy rules of the Health Insurance Portability and Accountability Act (HIPAA).

Authorization Statement

I, (Patient's Name) , authorize my prescribing physician,
(Prescriber's Name)
(Prescriber's Address)

caregiver and other sources, as deemed necessary to disclose such PHI provided to Duramed Pharmaceuticals, Inc., its affiliated companies and subcontractors on a need to know basis for purposes of administering the program for the duration of my participation in the program.

I understand that Duramed Pharmaceuticals, Inc., its affiliated companies and subcontractors will protect the information received in accordance with HIPAA and the other relevant State and Federal privacy laws. I further understand that this authorization permits Duramed Pharmaceuticals, Inc., its affiliates and subcontractors to share my PHI with individuals or entities who are not bound by the privacy requirements of HIPAA and that once in their possession, my PHI could be used or re-disclosed in a way no longer protected by HIPAA.

I understand that I may revoke this authorization, in writing, at any time by addressing such revocation to my prescribing physician and/or caregiver and that only a written revocation addressed to such person will constitute an effective withdrawal of my authorization.

Required Signature

_____ _____
Signature of patient or legal representative Date

If signed by patient's legal representative, complete the following:

Print name of legal representative: _____

Describe representative's authority to act for patient: _____

****

Important:

To the Patient:

Once you have completed and signed this authorization form, please give it to your prescriber. Do not send it to the Enjuvia™ Patient Assistance Program. Retain a copy for your records.

To the Prescriber:

Retain a copy of the Patient Authorization to Disclose Protected Health Information for your records. Please return the original copy of this signed form along with the completed Qualification application form to the Enjuvia™ Patient Assistance Program, 250 Phillips Blvd, Ste 250, Ewing, NJ 08618, or fax to 1.800.685.2577.

NM

Enjuvia™

(synthetic conjugated estrogens, B) Tablets

℞ only

Brief Summary (See package brochure for full prescribing information)

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.

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 in-crease 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 hypertriglyceridema, 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 T_4 and T_3 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), 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. 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 HDL_2 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 by Body System/Adverse Events*. **Body as a Whole-** Abdominal Pain, Accidental Injury, Flu Syndrome, Headache, Pain; **Digestive System-** Flatulence, Nausea; **Nervous System-** Dizziness, Paresthesia; **Respiratory System-** Bronchitis, Rhinitis, Sinusitis; **Urogenital System-** Breast Pain, Dysmenorrhea, Vaginitis. (*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.

DURAMED PHARMACEUTICALS, INC., Subsidiary of Barr Pharmaceuticals, Inc., Pomona, New York 10970
Revised SEPTEMBER 2005
BR-406, 407, 408, 410