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## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**BIJUVA (estradiol and progesterone) capsules, for oral use**
**Initial U.S. Approval: 2018**

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

***See full prescribing information for complete boxed warning.***

**Estrogen Plus Progestin Therapy**

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI) (5.1)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)**
- **The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age of older (5.3)**

**Estrogen-Alone Therapy**

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The WHI estrogen-alone substudy reported increased risks of stroke and DVT (5.1)**
- **The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older (5.3)**

### INDICATIONS AND USAGE

BIJUVA is a combination of an estrogen and progesterone indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause. (1.1)

### DOSAGE AND ADMINISTRATION

Take one capsule orally each evening with food. (2.1)

### DOSAGE FORMS AND STRENGTHS

BIJUVA (estradiol and progesterone) capsules contain 1 mg estradiol/100 mg progesterone. (3)

### CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.2)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or 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 with BIJUVA (4, 5.15)
- Known liver impairment or disease (4, 5.10)
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

### WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid replacement hormone therapy (5.11, 5.18)

### ADVERSE REACTIONS

In a single, prospective, randomized, placebo-controlled, double-blind trial, the most common adverse reactions with BIJUVA (estradiol and progesterone) capsules (incidence ≥ 3% of women and greater than placebo) were breast tenderness, headache, vaginal bleeding, vaginal discharge and pelvic pain. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact TherapeuticsMD, Inc at 1-888-228-0150 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

### DRUG INTERACTIONS

Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration. (7.1)

### USE IN SPECIFIC POPULATIONS

- Geriatric use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (5.3, 8.5)

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

**Revised: 10/2018**

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# FULL PRESCRIBING INFORMATION

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

**Estrogen Plus Progestin Therapy**

### Cardiovascular Disorders and Probable Dementia

**Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.4, 14.5)]*.**

**The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.4)]*.**

**The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age of older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.5)]*.**

### Breast Cancer

**The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.2), and Clinical Studies (14.4)]*.**
**In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.**

**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.**

**Estrogen-Alone Therapy**

### Endometrial Cancer

**There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.2)]*.**

### Cardiovascular Disorders and Probable Dementia

**Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.4, 14.5)]*.**
**The WHI estrogen-alone substudy reported increased risks of stroke and DVT in**

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**postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral CE (0.625 mg)-alone, relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.4)]*.**

**The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal *women [see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.5)]*.**

**In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens. 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.**

# 1 INDICATIONS AND USAGE

## 1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause.

# 2 DOSAGE AND ADMINISTRATION

Use of estrogen, alone or in combination with a progestogen, should be limited to the lowest effective dose available and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be reevaluated periodically as clinically appropriate to determine if treatment is still necessary.

## 2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause.

Take a single BIJUVA (estradiol and progesterone) capsule, 1 mg/100 mg, orally each evening with food.

# 3 DOSAGE FORMS AND STRENGTHS

BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are oval shaped, opaque, light pink on one side and dark pink on the other side, and printed with “1C1” in white ink.

# 4 CONTRAINDICATIONS

BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of cancer of the breast
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or history of these conditions

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- Active arterial thromboembolic disease (for example, stroke, MI), or a history of these conditions
- Known anaphylactic reaction, angioedema, or hypersensitivity to BIJUVA or any of its ingredients
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders

# 5 WARNINGS AND PRECAUTIONS

## 5.1 Cardiovascular Disorders

An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. An increased risk of stroke and DVT has been reported with estrogen-alone therapy. Should these occur or be suspected, therapy should be discontinued immediately.

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

*Stroke*

In the Women's Health Initiative estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.4)]*. The increase in risk was demonstrated after the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.4)]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

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

*Coronary Heart Disease*

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.4)]*.

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In the WHI estrogen-alone substudy, no overall effect on CHD events was reported in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.4)]*.

Subgroup analysis of women 50 to 59 years of age suggests a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

*Venous Thromboembolism*

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and PE) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[3] *[see Clinical Studies (14.4)]*. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

In the WHI estrogen-alone substudy, the risk of VTE was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[4] *[see Clinical Studies (14.4)]*. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

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.

### 5.2 Malignant Neoplasm

*Breast Cancer*

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per

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10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[5] *[see Clinical Studies (14.4)]*.

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80][6] *[see Clinical Studies (14.4)]*.

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

In a one-year trial, among 1684 women who received a combination of estradiol plus progesterone (1 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 50 mg progesterone or 0.25 mg estradiol plus 50 mg progesterone) or placebo (n=151), six new cases of breast cancer were diagnosed, two of which occurred among the group of 415 women treated with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg. No new cases of breast cancer were diagnosed in the group of 151 women treated with placebo.

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.

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*Endometrial Cancer*

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1 percent or less with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-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 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestogen therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

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 therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

*Ovarian Cancer*

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95% confidence interval [CI], 0.77 to 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7]

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

## 5.3 Probable Dementia

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95% CI, 1.21 to 3.48). The

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absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.5)]*.

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95% CI, 0.83 to 2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.5)]*.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI, 1.19 to 2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.5)]*.

## 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. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

## 5.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is a 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 permanently discontinued.

## 5.7 Addition of a Progestogen 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 progestogen with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

## 5.8 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

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## 5.9 Hypertriglyceridemia

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

## 5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women 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.

## 5.11 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. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

## 5.12 Fluid Retention

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

## 5.13 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

## 5.14 Exacerbation of Endometriosis

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

## 5.15 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

## 5.16 Exacerbation of Other Conditions

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

## 5.17 Laboratory Tests

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

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## 5.18 Drug Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor 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 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 concentrations, increased triglyceride levels.

Impaired glucose tolerance.

# 6 ADVERSE REACTIONS

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

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

The safety of estradiol and progesterone capsules was assessed in a 1-year, Phase 3 trial that included 1,835 postmenopausal women (1684 were treated with estradiol and progesterone capsules once daily and 151 women received placebo). Most women (~70%) in the active treatment groups were treated for ≥ 326 days.

Treatment related adverse reactions with an incidence of ≥ 3% in the BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, group and numerically greater than those reported in the placebo group are listed in Table 1.

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**Table 1: Treatment-Emergent Adverse Reactions Reported at a Frequency of ≥ 3% and Numerically More Common in Women Receiving BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg**

| Preferred Term | BIJUVA 1 mg/100 mg (N=415) | Placebo (N=151) |
|---|---|---|
| Breast tenderness | 43 (10.4) | 1 (0.7) |
| Headache | 14 (3.4) | 1 (0.7) |
| Vaginal bleeding | 14 (3.4) | 0 |
| Vaginal discharge | 14 (3.4) | 1 (0.7) |
| Pelvic pain | 13 (3.1) | 0 |

# 7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with BIJUVA.

## 7.1 Metabolic Interactions

*Effects of Other Drugs on Estrogens and Progestins*

In-vitro and in-vivo studies have shown that estrogens and progestins are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen and progestin drug metabolism. Inducers of CYP3A4 such as St. John's wort (Hypericum perforatum) preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens and progestins, 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 the estrogen or the progestin or both and may result in side effects.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

**Risk Summary**

BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are not indicated for use in pregnancy. There are no data with the use of BIJUVA in pregnant women, however, epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to combined hormonal contraceptives (estrogen and progestins) before conception or during early pregnancy.

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## 8.2 Lactation

**Risk Summary**

BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are not indicated for use in females of reproductive potential. Estrogens are present in human milk and can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established.

## 8.4 Pediatric Use

BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are not indicated in children. Clinical studies have not been conducted in the pediatric population.

## 8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, to determine whether those over 65 years of age differ from younger women in their response to BIJUVA.

*The Women's Health Initiative Studies*

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.4)]*.

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.4)]*.

*The Women's Health Initiative Memory Study*

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen plus progestin or estrogen-alone when compared to placebo *[see Warnings and Precautions (5.3), and Clinical Studies (14.5)]*.

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Warnings and Precautions (5.3), and Clinical Studies (14.5)]*.

# 10 OVERDOSAGE

Overdosage of estrogen plus progestogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, therapy with institution of appropriate symptomatic care.

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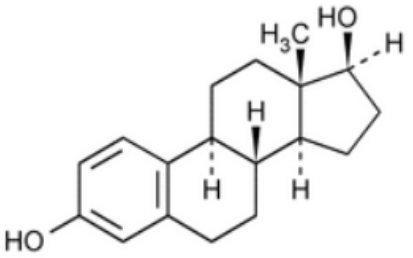
# 11 DESCRIPTION

BIJUVA (estradiol and progesterone) is an oval shaped opaque capsule, which is light pink on one side and dark pink on the other side, and printed with “1C1” in white ink.

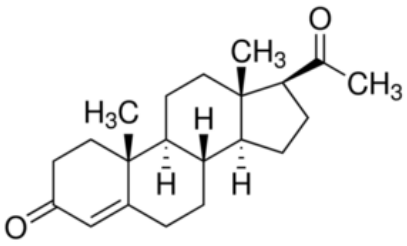
Estradiol (estra-1,3,5 (10)-triene-3,17β-diol), an estrogen, has a molecular weight of 272.38, and chemical formula $C_{18}H_{24}O_2$.

Progesterone (pregn-4-ene-3, 20-dione) has a molecular weight of 314.47, and chemical formula $C_{21}H_{30}O_2$.

The structural formulas are as follows:




Estradiol




Progesterone

Each BIJUVA (estradiol and progesterone) capsule, 1 mg/100 mg, contains the following inactive ingredients: ammonium hydroxide, ethanol, ethyl acetate, FD&C Red #40, gelatin, glycerin, hydrolyzed gelatin, isopropyl alcohol, lauroyl polyoxyl-32 glycerides, lecithin, medium chain mono and di-glycerides, medium chain triglycerides, polyethylene glycol, polyvinyl acetate phthalate, propylene glycol, purified water, and titanium dioxide.

# 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

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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 seen in postmenopausal women.

Endogenous progesterone is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium.

Progesterone enhances cellular differentiation and generally opposes the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen. Progesterone exerts its effects in target cells by binding to specific progesterone receptors that interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus, and central nervous system.

## 12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg.

## 12.3 Pharmacokinetics

Absorption

The oral absorption of both estradiol and progesterone is subject to first pass metabolism. After multiple doses of BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, the $t_{max}$ (the time at which the maximum concentration is attained) for estradiol is approximately 5 hours and approximately 3 hours for progesterone (Figure 1, Figure 2, and Table 2, below). Steady state for both estradiol and progesterone components of BIJUVA, as well as estradiol's main metabolite, estrone, is achieved within seven days.

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**Figure 1: Mean Steady-State Serum Estradiol Concentrations Following Daily Oral Administration of 1 mg Estradiol/100 mg Progesterone (Baseline Unadjusted, at Day 7)**

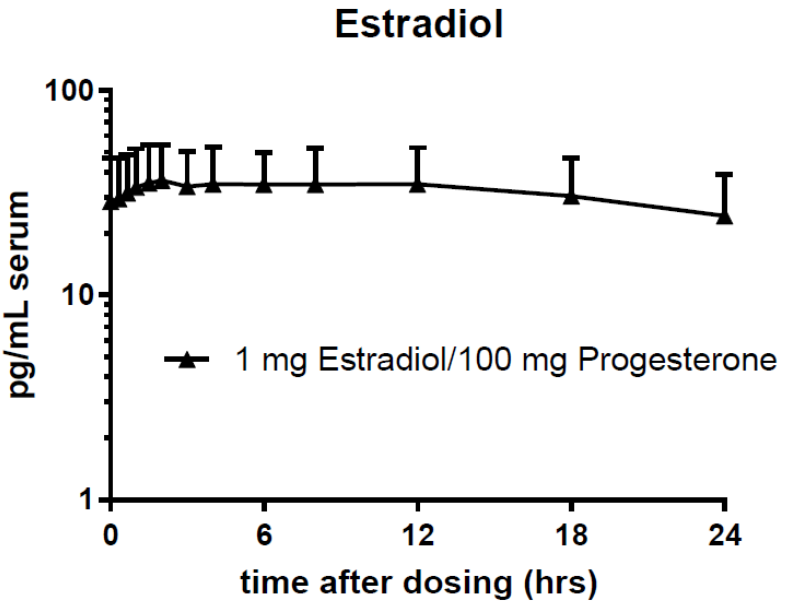


**Figure 2: Mean Steady-State Serum Progesterone Concentrations Following Daily Oral Administration of 1 mg Estradiol/100 mg Progesterone (Baseline Unadjusted, at Day 7)**

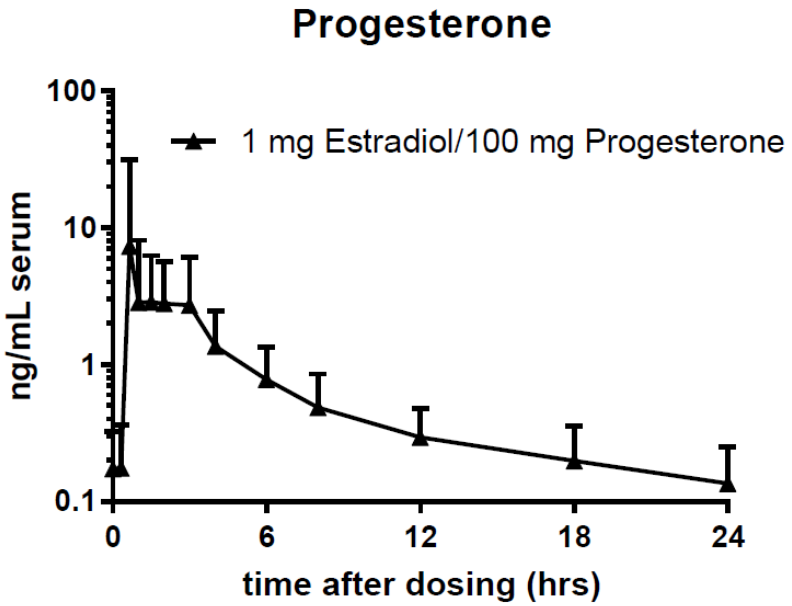

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**Table 2: Mean (SD) Steady-State Pharmacokinetic Parameters after Administration of Capsules Containing 1 mg Estradiol/100 mg Progesterone in Healthy Postmenopausal Women (Baseline Unadjusted, at Day 7)**

| **Dosage Strength (estradiol/progesterone)** | **BIJUVA 1 mg/100 mg Mean (SD)** | |
|---|---|---|
| **Estradiol** | **N** | |
| $AUC_{0-\tau}$ (pg·h/mL) | 20 | 772.4 (384.1) |
| $C_{max}$ (pg/mL) | 20 | 42.27 (18.60) |
| $C_{avg}$ (pg/mL) | 19 | 33.99 (14.53) |
| $t_{max}$ (h) | 19 | 4.93(4.97) |
| $t_{½}$ (h)* | 19 | 26.47 (14.61) |
| **Estrone** | | |
| $AUC_{0-\tau}$ (pg·h/mL) | 20 | 4594 (2138) |
| $C_{max}$ (pg/mL) | 20 | 238.5 (100.4) |
| $C_{avg}$ (pg/mL) | 20 | 192.1 (89.43) |
| $t_{max}$ (h) | 20 | 5.45 (3.47) |
| $t_{½}$ (h)* | 19 | 22.37 (7.64) |
| **Progesterone** | | |
| $AUC_{0-\tau}$ (ng·h/mL) | 20 | 18.05 (15.58) |
| $C_{max}$ (ng/mL) | 20 | 11.31 (23.10) |
| $C_{avg}$ (ng/mL) | 20 | 0.76 (0.65) |
| $t_{max}$ (h) | 20 | 2.64 (1.51) |
| $t_{½}$ (h) | 18 | 9.98 (2.57) |

*Effective t½. Calculated as 24•ln(2)/ ln(accumulation ratio/(accumulation ratio-1)) for subjects with accumulation ratio >1.
Abbreviations: $AUC_{0-\tau}$ = area under the concentration vs time curve within the dosing interval at steady-state, $C_{avg}$ = average concentration at steady-state, $C_{max}$ = maximum concentration, SD = standard deviation, $t_{max}$ = time to maximum concentration, $t_{½}$ = half-life

*Food Effect*

Concomitant food ingestion increased the AUC and $C_{max}$ of the progesterone component of BIJUVA relative to a fasting state when administered at a dose of 100 mg. In a study where BIJUVA was administered to postmenopausal women at a dose of 1 mg estradiol/100 mg progesterone within 30 minutes of starting a high-fat meal, the $C_{max}$ and AUC of progesterone were 162% and 79% higher, respectively, relative to the fasting state. Concomitant food ingestion had no effect on the AUC of the estradiol component of BIJUVA but decreased $C_{max}$ by approximately 54% and delayed $T_{max}$ to 12 hours.

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*Distribution*

**Estradiol**

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 circulating in the blood largely are bound to SHBG and albumin.

**Progesterone**

Progesterone is approximately 96% to 99% bound to serum proteins, primarily to serum albumin (50% to 54%) and transcortin (43% to 48%).

*Elimination*

Following repeat dosing with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, the half-life of estradiol was approximately 26 hours. The half-life of progesterone, following repeat dosing was approximately 10 hours.

*Metabolism*

**Estradiol**

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, 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.

**Progesterone**

Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites, which are excreted in the bile, may be deconjugated and may be further metabolized in the intestine via reduction, dehydroxylation, and epimerization.

*Excretion*

**Estradiol**

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

**Progesterone**

The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. Progesterone metabolites are eliminated mainly by the kidneys. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.

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# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nonclinical toxicity studies to determine the potential of BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, to cause carcinogenicity or mutagenicity have not been performed. The effect of BIJUVA on fertility has not been evaluated in animals.

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.

Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors, and endometrial stromal sarcomas. In dogs, long-term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen.

Progesterone did not show evidence of genotoxicity in *in vitro* studies for point mutations or for chromosomal damage. *In vivo* studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg. Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would impair fertility until the cessation of treatment.

# 14 CLINICAL STUDIES

## 14.1 Effects on Vasomotor Symptoms

The effectiveness and safety of BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, on moderate to severe vasomotor symptoms (hot flushes) due to menopause were examined in a 12-week randomized, double-blind, placebo-controlled substudy of a single 52-week safety study. A total of 726 postmenopausal women were randomized to multiple dose combinations of estradiol and progesterone, and placebo; these women were 40 to 65 years of age (mean 54.6 years) and had at least 50 moderate to severe vasomotor symptoms per week at baseline. The mean number of years since last menstrual period was 5.9 years, with all women undergoing natural menopause. The primary efficacy population consisted of women who self-identified their race as: White (67%), Black/African American (31%), and “Other” (2.1%). In the substudy evaluating effects on moderate to severe vasomotor symptoms, a total of 141 women received BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, and 135 women received placebo.

The evaluated co-primary efficacy endpoints included: 1) mean weekly reduction in frequency of moderate to severe vasomotor symptoms with BIJUVA compared to placebo at Weeks 4 and 12; a clinically meaningful threshold for the reduction in frequency of vasomotor symptoms, defined as14 vasomotor symptoms per week above placebo, was applied, and 2) mean weekly reduction in severity of moderate to severe vasomotor symptoms with BIJUVA compared to placebo at Weeks 4 and 12.

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Overall, BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, statistically significantly reduced both the frequency and severity of moderate to severe vasomotor symptoms from baseline compared with placebo at Weeks 4 and 12. A clinically meaningful threshold of a reduction of 14 vasomotor symptoms per week above placebo was not demonstrated for BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, until Week 5. The change from baseline in the frequency and severity of vasomotor symptoms observed and the difference from placebo are shown in Table 3 and Table 4, respectively.

**Table 3: Mean Weekly Change from Baseline and Difference from Placebo in the Frequency of Moderate to Severe Vasomotor Symptoms**

| | **BIJUVA 1 mg/100 mg (N=141)** | **Placebo (N=135)** |
|---|---|---|
| **Week 4** | n=134 | n=126 |
| Baseline | 72.1 (27.80) | 72.3 (23.44) |
| Mean (SD) change from baseline | -40.6 (30.59) | -26.4 (27.05) |
| Difference from placebo* | -12.81 (3.30) | --- |
| P-value** | < 0.001 | --- |
| | | |
| **Week 12** | n=124 | n=115 |
| Baseline | 72.2 (25.04) | 72.2 (22.66) |
| Mean (SD) change from baseline | -55.1 (31.36) | -40.2 (29.79) |
| Difference from placebo* | -16.58 (3.44) | --- |
| P-value** | <0.001 | --- |

*Least square mean difference (SE) from placebo
**P-value of least square mean difference from placebo using mixed model repeated measures analyses
Definitions: SD – standard deviation; SE – standard error

**Table 4: Mean Weekly Change from Baseline and Difference from Placebo in the Severity of Moderate to Severe Vasomotor Symptoms**

| | **BIJUVA 1 mg/100 mg (N=141)** | **Placebo (N=135)** |
|---|---|---|
| **Week 4** | n=134 | n=126 |
| Baseline | 2.54 (0.325) | 2.52 (0.249) |
| Mean (SD) change from baseline | -0.48 (0.547) | -0.34 (0.386) |
| Difference from placebo* | -0.13 (0.061) | --- |
| P-value** | 0.031 | --- |
| | | |

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| | BIJUVA 1 mg/100 mg (N=141) | Placebo (N=135) |
|---|---|---|
| **Week 12** | n=124 | n=115 |
| Baseline | 2.55 (0.235) | 2.52 (0.245) |
| Mean (SD) change from baseline | -1.12 (0.963) | -0.56 (0.603) |
| Difference from placebo* | -0.57 (0.100) | --- |
| P-value** | <0.001 | --- |

*Least square mean difference (SE) from placebo
** P-value of least square mean difference from placebo using mixed model repeated measures analyses
Definitions: SD – standard deviation; SE – standard error

Adjusting for potential confounders such as BMI, smoking, alcohol use, and baseline estradiol level, treatment with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, did not demonstrate statistically significant reductions in both frequency and severity of moderate to severe vasomotor symptoms by Week 12 in women who self-identified as Black/African Americans (data not shown).

## 14.2 Effects on Endometrium

Effects of BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, on endometrial hyperplasia and endometrial malignancy were assessed in the 52-week safety trial. The Endometrial Safety population included women who had taken at least one dose of BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, and had baseline and post-baseline endometrial biopsies. During the trial, endometrial biopsy assessments revealed 1 case of endometrial hyperplasia and no cases of endometrial cancer in women who received BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, and no cases of hyperplasia or endometrial cancer in women who received placebo (see Table 5).

**Table 5: Incidence of Endometrial Hyperplasia After up to 12 Months of Treatment**

| | BIJUVA 1 mg/100 mg (N=281) | Placebo (N=92) |
|---|---|---|
| Hyperplasia incidence rate % (n/N) | 1/281 (0.36) | 0/92 (0.00) |
| One-sided upper 95% confidence limit | 1.97 | 3.93 |

Four (4) cases of disordered proliferative endometrium were also reported for BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, in the 52-week safety trial.

## 14.3 Effects on Uterine Bleeding or Spotting

Uterine bleeding or spotting was evaluated in the 52-week safety study by daily diary. At 52 weeks, cumulative amenorrhea was reported by 56.1% of women who received BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, and 78.9% who received placebo.

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## 14.4 Women's Health Initiative Studies

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

*WHI Estrogen Plus Progestin Substudy*

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9% White, 6.8% Black, 5.4% Hispanic, 3.9% Other) are presented in Table 6. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

**Table 6: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]**

| Event | Relative Risk CE/MPA vs Placebo (95% nCI[c]) | CE/MPA n=8,506 | Placebo n=8,102 |
|---|---|---|---|
| | | Absolute Risk per 10,000 Women-Years | |
| CHD events | 1.23 (0.99-1.53) | 41 | 34 |
| *Non-fatal MI* | *1.28 (1.00-1.63)* | *31* | *25* |
| *CHD death* | *1.10 (0.70-1.75)* | *8* | *8* |
| All Strokes | 1.31 (1.03-1.68) | 33 | 25 |
| *Ischemic stroke* | *1.44 (1.09-1.90)* | *26* | *18* |
| Deep vein thrombosis[d] | 1.95 (1.43-2.67) | 26 | 13 |
| Pulmonary embolism | 2.13 (1.45-3.11) | 18 | 8 |
| Invasive breast cancer[e] | 1.24 (1.01-1.54) | 41 | 33 |
| Colorectal cancer | 0.61 (0.42-0.87) | 10 | 16 |

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| Event | Relative Risk CE/MPA vs Placebo (95% nCI[c]) | CE/MPA n=8,506 | Placebo n=8,102 |
|---|---|---|---|
| | | Absolute Risk per 10,000 Women-Years | |
| Endometrial cancer[d] | 0.81 (0.48-1.36) | 6 | 7 |
| Cervical cancer[d] | 1.44 (0.47-4.42) | 2 | 1 |
| Hip fracture | 0.67 (0.47-0.96) | 11 | 16 |
| Vertebral fractures[d] | 0.65 (0.46-0.92) | 11 | 17 |
| Lower arm/wrist fractures[d] | 0.71 (0.59-0.85) | 44 | 62 |
| Total fractures[d] | 0.76 (0.69-0.83) | 152 | 199 |
| Overall Mortality[c,f] | 1.00 (0.83-1.19) | 52 | 52 |
| Global Index[g] | 1.13 (1.02-1.25) | 184 | 165 |

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Results are based on centrally adjudicated data.
[c] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[d] Not included in "global index".
[e] Includes metastatic and non-metastatic breast cancer with the exception of *in situ* 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 plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50-59 years of age, a non-significant trend toward reduced risk for overall mortality [HR 0.69 (95 percent CI, 0.44-1.07)].

*WHI Estrogen-Alone Substudy*

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% percent Other) after an average follow-up of 7.1 years, are presented in Table 7.

**Table 7: Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI[a]**

| Event | Relative Risk CE vs Placebo (95% nCI[b]) | CE n=5,310 | Placebo n=5,429 |
|---|---|---|---|
| | | Absolute Risk per 10,000 Women-Years | |
| CHD events[c] | 0.95 (0.78-1.16) | 54 | 57 |
| *Non-fatal MI[c]* | *0.91 (0.73-1.14)* | *40* | *43* |
| *CHD death[c]* | *1.01 (0.71-1.43)* | *16* | *16* |

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| Event | Relative Risk CE vs Placebo (95% nCI[b]) | CE n=5,310 | Placebo n=5,429 |
|---|---|---|---|
| | | Absolute Risk per 10,000 Women-Years | |
| All Strokes[c] | 1.33 (1.05-1.68) | 45 | 33 |
| *Ischemic stroke*[c] | *1.55 (1.19-2.01)* | *38* | *25* |
| Deep vein thrombosis[c,d] | 1.47 (1.06-2.06) | 23 | 15 |
| Pulmonary embolism[c] | 1.37 (0.90-2.07) | 14 | 10 |
| Invasive breast cancer[c] | 0.80 (0.62-1.04) | 28 | 34 |
| Colorectal cancer[c] | 1.08 (0.75-1.55) | 17 | 16 |
| Hip fracture[c] | 0.65 (0.45-0.94) | 12 | 19 |
| Vertebral fractures[c,d] | 0.64 (0.44-0.93) | 11 | 18 |
| Lower arm/wrist fractures[c,d] | 0.58 (0.47-0.72) | 35 | 59 |
| Total fractures[c,d] | 0.71 (0.64-0.80) | 144 | 197 |
| Death due to other causes[e,f] | 1.08 (0.88-1.32) | 53 | 50 |
| Overall mortality[c,d] | 1.04 (0.88-1.22) | 79 | 75 |
| Global Index[g] | 1.02 (0.92-1.13) | 206 | 201 |

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[c] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[d] Not included in "global index".
[e] Results are based on an average follow-up of 6.8 years.
[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
[g] A subset of the events was combined in a “global index”, defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI “global index” that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.[9] The absolute excess risk of events included in the “global index” was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI, and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined.[10]

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Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy, stratified by age, showed in women 50-59 years of age a non-significant trend toward reduced risk for CHD *[hazard ratio (HR) 0.63 (95% CI, 0.36 to 1.09)]* and overall mortality *[HR 0.71 (95% CI, 0.46 to 1.11)]*.

## 14.5 Women's Health Initiative Memory Study

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were 65 to 69 years of age; 35% were 70 to 74 years; 18% were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95% CI, 1.21 to3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD), and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominately healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45% were 65 to 69 years of age; 36% were 70 to 74 years of age; 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.

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 to 2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included AD, VaD, and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5*)].

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI, 1.19 to 2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

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# 16 HOW SUPPLIED/STORAGE AND HANDLING

## 16.1 How Supplied

BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are oval-shaped opaque capsules, which are light pink on one side and dark pink on the other side. Each capsule is imprinted in white ink indicating the dosage strength (1C1). BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are provided in a blister package of 30 capsules.

BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg NDC 50261-211-30

Keep out of reach of children. Packages are not child-resistant.

## 16.2 Storage and Handling

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

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# 17 PATIENT COUNSELING INFORMATION

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

## Abnormal Vaginal Bleeding

Inform postmenopausal women of the importance of reporting abnormal vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.2)]*.

## Possible Serious Adverse Reactions with Estrogen Plus Progesterone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen plus progesterone therapy including cardiovascular disorders, malignant neoplasms, and probable dementia *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

## Possible Less Serious but Common Adverse Reactions with Estrogen Plus Progesterone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen plus progesterone therapy such as breast tenderness, headache, vaginal discharge, and pelvic pain [*see Adverse Reactions (6.1)]*.

## Missed Evening Dose of BIJUVA

Advise the patient that if she misses her evening dose, she should take the dose with food as soon as she can, unless it is within two hours of the next evening dose.

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PATIENT INFORMATION

BIJUVA (bī joo' vah)

(estradiol and progesterone)

capsules, for oral use

**What is the most important information I should know about BIJUVA?**

- Do not use estrogens with or without progestogens to prevent heart disease, heart attacks, strokes, or dementia (decline of brain function).
- Taking estrogens with progestogens may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Taking estrogens with progestogens may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- Taking estrogen-alone may increase your chance of getting cancer of the uterus.
- Taking estrogen-alone may increase your chances of getting strokes or blood clots.
- Taking estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age or older.
- You and your healthcare provider should talk regularly about whether you still need treatment with BIJUVA.

**What is BIJUVA?**

- BIJUVA is a prescription medicine that contains two kinds of hormones, an estrogen and progesterone.

**What is BIJUVA used for?**

BIJUVA is used after menopause to **reduce moderate to severe hot flashes**.

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

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

**Who should not take BIJUVA?**

**Do not take BIJUVA if you have had your uterus (womb) removed (hysterectomy).**

BIJUVA contains progesterone to decrease the chance of getting cancer of the uterus. If you do not have a uterus, you do not need progesterone and you should not take BIJUVA.

**Do not take BIJUVA if you:**

- **have any unusual vaginal bleeding.**
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **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 have had cancer, talk with your healthcare provider about whether you should take BIJUVA.
- **currently have or have had blood clots.**
- **had a stroke or heart attack.**
- **currently have or have had liver problems.**
- **have been diagnosed with a bleeding disorder.**
- **are allergic to BIJUVA or any of its ingredients.** See the list of ingredients in BIJUVA at the end of this leaflet.

**Before you take BIJUVA, tell your healthcare provider about all of your medical conditions, including if you:**

- **have high levels of fat in your blood (triglycerides).**
- **have any unusual vaginal bleeding.** Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **have certain medical conditions that may become worse while you are taking BIJUVA.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as:

  - o asthma (wheezing)
  - o diabetes
  - o epilepsy (seizures)
  - o migraine

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- a genetic problem called porphyria
- lupus
- hypertension (high blood pressure)
- have high calcium in your blood
- endometriosis
- angioedema (swelling of face or tongue)
- problems with your heart, liver, thyroid or kidneys

- **are going to have surgery or will be on bed rest.** Your healthcare provider will let you know if you need to stop taking BIJUVA.
- **are pregnant or think you may be pregnant.** BIJUVA is not for pregnant women.
- **are breastfeeding.** The hormones in BIJUVA can pass into your breast milk.

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may affect how BIJUVA works. Some other medicines and food products may increase or decrease the concentrations of the hormones in BIJUVA in the blood. BIJUVA may affect how your other medicines work, and other medicines may affect how BIJUVA works.

**How should I take BIJUVA?**

- Take BIJUVA exactly as your healthcare provider tells you to take it.
- Take 1 capsule by mouth each evening with food.
- If you miss a dose of BIJUVA, take the missed dose as soon as possible with food, unless it is within two hours of the next evening dose of BIJUVA.
- Estrogens should be used at the lowest dose possible for your treatment and 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 BIJUVA.

**What are the possible side effects of BIJUVA?**

**Side effects are grouped by how serious they are and how often they happen when you are treated. Serious but less common side effects include:**

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

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

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

**The most common side effects of BIJUVA include:**

- breast tenderness
- headache
- vaginal bleeding
- vaginal discharge
- pelvic pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all of the possible side effects of BIJUVA. Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to TherapeuticsMD® at 1-888-228-0150.

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**For current labeling information, please visit https://www.fda.gov/drugsatfda**

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

- Talk with your healthcare provider regularly about whether you should continue taking BIJUVA.
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestogen is right for you.
- The addition of a progestogen is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb).
- See your healthcare provider right away if you get vaginal bleeding while taking BIJUVA.
- 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 (breast X-ray), 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 for getting heart disease.

**How should I store BIJUVA?**

- Store at room temperature between 68°F to 77°F (20°C to 25ºC).
- **Keep BIJUVA and all medicines out of the reach of children.**

**General information about the safe and effective use of BIJUVA.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BIJUVA for a condition for which it was not prescribed. Do not give BIJUVA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about BIJUVA that is written for health professionals.

**What are the ingredients in BIJUVA?**

**Active ingredient**s: estradiol and progesterone

**Inactive ingredients**: ammonium hydroxide, ethanol, ethyl acetate, FD&C Red #40, gelatin, glycerin, hydrolyzed gelatin, isopropyl alcohol, lauroyl polyoxyl-32 glycerides, lecithin, medium chain mono and di-glycerides, medium chain triglycerides, polyethylene glycol, polyvinyl acetate phthalate, propylene glycol, purified water, and titanium dioxide.

BIJUVA is supplied in blister cartons of 30 capsules.

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Manufactured for:
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Boca Raton, FL 33487

Manufactured by:
Catalent Pharma Solutions, LLC
St Petersburg, FL 33716

(label control number to be added)

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 10/2018