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

RECENT MAJOR CHANGES

Boxed Warning, Cardiovascular Disorders, Probable Dementia, Breast Cancer, and Endometrial Cancer	removed 2/2026
Dosage and Administration (2)	2/2026
Contraindications (4)	2/2026
Warnings and Precautions, Cardiovascular Disorders (5.1)	2/2026
Warnings and Precautions, Malignant Neoplasms (5.2)	2/2026
Warnings and Precautions, Probable Dementia	removed 2/2026
Warnings and Precautions, Addition of a Progestogen When a Woman Has Not Had a Hysterectomy	removed 2/2026

INDICATIONS AND USAGE

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

One capsule orally each evening with food. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 0.5 mg estradiol/100 mg progesterone or 1 mg estradiol/100 mg progesterone. (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4, 5.2)
- Breast cancer or a history of breast cancer (4, 5.2)
- Estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or 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, angioedema, or hypersensitivity to BIJUVA (4, 5.15)
- Hepatic impairment or disease (4, 5.8)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

WARNINGS AND PRECAUTIONS

- Cardiovascular Disorders: Increased risks of PE, DVT, stroke, and MI are reported with estrogen plus progestin therapy. Manage risk factors for arterial vascular disease and/or venous thromboembolisum. Discontinue if an arterial or venous thrombotic or thromboembolic event occurs. (5.1)
- Malignant Neoplasms: Assess risk and provide surveillance measures for breast cancer, such as breast examinations and mammography. (5.2)
- Estrogens increase the risk of gallbladder disease. (5.3)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs. (5.4, 5.5, 5.7, 5.8)
- Monitor thyroid function in women on thyroid replacement hormone therapy. (5.9, 5.15)

ADVERSE REACTIONS

The most common adverse reactions with BIJUVA (incidence ≥ 3% of women and greater than placebo) are: breast tenderness, headache, nausea, vaginal bleeding, vaginal discharge and pelvic pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact M a y n e P h a r m a at 1-844-825-8500 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)

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

Revised: 2/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause

2 DOSAGE AND ADMINISTRATION

The timing of BIJUVA initiation can affect the overall risk-benefit profile. Consider initiating BIJUVA in women < 60 years old or < 10 years from onset of menopause *[see Warnings and Precautions (5), Adverse Reactions (6.1), Use in Specific Populations (8.5) and Clinical Studies (14)]*.

Take a single BIJUVA capsule orally each evening with food. Generally, start therapy with BIJUVA 0.5 mg estradiol/100 mg progesterone dosage strength. Make dosage adjustment based on the clinical response. Attempt to taper or discontinue BIJUVA at 3 to 6 month intervals.

3 DOSAGE FORMS AND STRENGTHS

BIJUVA capsules, 0.5 mg/100 mg, are oval shaped, opaque, light pink on one side, dark pink on the other side, and printed with "5C1" in white ink.

BIJUVA capsules, 1 mg/100 mg, are oval shaped, opaque, light pink on one side, dark pink on the other side, and printed with "1C1" in white ink.

4 CONTRAINDICATIONS

BIJUVA is contraindicated in women with any of the following conditions:

- Abnormal genital bleeding of unknown etiology *[see Warnings and Precautions (5.2)]*.
- Breast cancer or a history of breast cancer *[see Warnings and Precautions (5.2)]*.
- Estrogen-dependent neoplasia *[see Warnings and Precautions (5.2)]*.
- Active deep vein thrombosis (DVT), pulmonary embolisum (PE), or history of these conditions *[see Warnings and Precautions (5.1)]*.
- Active arterial thromboembolic disease (for example, stroke, myocardial infarction (MI)), or a history of these conditions *[see Warnings and Precautions (5.1)]*.
- Known anaphylactic reaction, angioedema, or hypersensitivity to BIJUVA.
- Hepatic impairment or disease *[see Warnings and Precautions (5.8)]*
- Known thrombophilic disorders, such as protein C, protein S, or antithrombin deficiency

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

BIJUVA is contraindicated in females with active DVT, PE, arterial thromboembolic disease (e.g., stroke, MI) disease, or a history of these conditions *[see Contraindications (4)]*. Immediately discontinue BIJUVA if a PE, DVT, stroke, or MI occurs or is suspected.

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

The safety and efficacy of BIJUVA for the prevention of cardiovascular disorders has not been established *[see Clinical Studies (14.4)]*.

The Women's Health Initiative (WHI) estrogen plus progestin trial reported increased risks of PE, DVT, stroke, and MI in postmenopausal women (50 to 79 years of age, average age 63.4 years) during the 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. Analyses were also conducted in women aged 50-59 years, a group of women more likely to present with new onset of moderate to severe VMS compared to women in other age groups in the trial *[see Clinical Studies (14.4)]*.

Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin trial of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products.

Venous Thromboembolism

In women aged 50-59 years, the WHI estrogen plus progestin trial reported a relative risk for PE of 2.05 (95% confidence interval [CI], 0.89-4.71) for CE/MPA compared to placebo, with a risk difference of 6 per 10,000 women-years (WYs; 11 versus 5). The relative risk for DVT was 3.01 (95% CI, 1.36-6.66) in those receiving CE/MPA compared to placebo, with a risk difference of 10 per 10,000 WYs (15 versus 5) *[see Clinical Studies (14.4)]*.

In the overall study population of women aged 50-79 years (average 63.4 years), the trial reported a relative risk for PE of 1.98 (95% CI, 1.36-2.87) for CE/MPA compared to placebo, with a risk difference of 9 per 10,000 WYs (18 versus 9). The relative risk for DVT was 1.87 (95% CI, 1.37-2.54) for CE/MPA compared to placebo, with a risk difference of 12 per 10,000 WYs (25 versus 14) *[see Clinical Studies (14.4)]*.

Stroke

In women aged 50-59 years, the WHI estrogen plus progestin trial reported a relative risk for stroke of 1.51 (95% CI, 0.81-2.82) for CE/MPA compared to placebo, with a risk difference of 5 per 10,000 WYs (15 versus 10) *[see Clinical Studies (14.4)]*.

In the overall study population of women aged 50-79 years (average 63.4 years), the WHI estrogen plus progestin trial reported relative risk for stroke of 1.37 (95% CI, 1.07-1.76) for CE/MPA compared to placebo, with a risk difference of 9 per 10,000 WYs (33 versus 24) *[see Clinical Studies (14.4)]*.

Coronary Heart Disease

In women 50 to 59 years of age, the WHI estrogen plus progestin trial reported a relative risk for coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) of 1.34 (95% CI, 0.82-2.19) for CE/MPA compared placebo, with a risk difference of 5 per 10,000 WYs (23 versus 17).

In the overall study population of women aged 50-79 years (average 63.4 years), the trial reported a relative risk of CHD of 1.18 (95% CI, 0.95-1.45) for CE/MPA compared to placebo, with a risk difference of 6 per 10,000 WYs (41 versus 35) *[see Clinical Studies (14.4)]*.

In the Heart and Estrogen/Progestin Replacement Study (HERS) and open label extension (HERS II), postmenopausal women with documented heart disease (n=2,763, average age 66.7 years) received daily CE (0.625 mg) plus MPA or placebo. In Year 1, there were more CHD events in the CE plus MPA-treated group than placebo; however, rates of CHD events were comparable among both groups for the remainder of the duration of the studies (average total follow-up of 6.8 years).[2, 3]

5.2 Malignant Neoplasms

Breast Cancer

BIJUVA is contraindicated in women with breast cancer, a history of breast cancer, or estrogen-dependent neoplasia [see Contraindications (4)].

Discontinue BIJUVA if a hormone-sensitive malignancy is diagnosed.The use of estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

Only daily oral CE 0.625 mg and MPA 2.5 mg were studied in the estrogen plus progestin trial of the WHI. Therefore, the relevance of the WHI findings regarding breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for

other products.

In women 50-59 years of age, the WHI estrogen plus progestin trial reported a relative risk for invasive breast cancer of 1.21 (95% CI, 0.81-1.80) for CE/MPA compared to placebo, with a risk difference of 6 per 10,000 WYs (33 versus 27). In this age group, among those who reported no prior use of hormone therapy, the relative risk was 1.06 (95% CI, 0.67-1.67) for CE/MPA compared to placebo, with a risk difference of 2 per 10,000 WYs (33 versus 31) *[see Clinical Studies (14.4)]*.

In the overall study population of women aged 50-79 years (average 63.4 years), the WHI estrogen plus progestin trial reported a relative risk for invasive breast cancer of 1.24 (95% CI, 1.01-1.53) for CE/MPA compared to placebo, with a risk difference of 9 per 10,000 WYs (43 versus 35). In the overall study population, among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.85 (95% CI, 1.18-2.90) for CE/MPA compared to placebo, with a risk difference of 21 per 10,000 WYs (46 versus 25). Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09 (95% CI, 0.86-1.39), with a risk difference of 4 per 10,000 WYs (40 versus 36). Invasive breast cancers were larger, were more likely to be node positive, and were 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. Extension of the WHI trial also demonstrated increased breast cancer risk associated with estrogen plus progestin therapy *[see Clinical Studies (14.4)]*.[1]

Consistent with the WHI trial, observational studies have also reported an increased risk of breast cancer with estrogen plus progestin therapy. A large meta-analysis including 24 prospective studies of postmenopausal women comparing current use of estrogen plus progestin products with use duration of 5 to 14 years (average of 9 years) versus never use reported a relative risk for breast cancer of 2.08 (95% CI, 2.02-2.15). These studies have not generally found the risk of breast cancer to be different among the various estrogen plus progestin combinations, doses, or routes of administration.[4]

Regarding breast cancer mortality, the WHI estrogen plus progestin trial did not show a statistically significant difference between CE/MPA and placebo. The trial reported a relative risk of 1.35 (95% CI, 0.94-1.95) for CE/MPA compared to placebo, with a risk difference of 1 per 10,000 WYs (5 versus 4) after a median of 19 years of cumulative follow-up *[see Clinical Studies (14.4)]*.

Ovarian Cancer

Comparing CE/MPA to placebo, women 50-59 years of age had a relative risk for ovarian cancer of 0.30 (95% CI, 0.06-1.47) and the risk difference was -3 per 10,000 WYs (1 versus 4) *[see Clinical Studies (14.4)]*.

In the overall WHI study population of women aged 50-79 years (average 63.4 years), the WHI estrogen plus progestin trial reported a relative risk for ovarian cancer of 1.41 (95% CI, 0.75-2.66) for CE/MPA versus placebo after an average follow-up of 5.6 years. The risk difference was 1 per 10,000 WYs (5 versus 4) *[see Clinical Studies (14.4)]*.

A large meta-analysis including 17 prospective studies of postmenopausal women compared current use of estrogen plus progestin products versus never use and reported a relative risk for ovarian cancer of 1.37 (95% CI, 1.26-1.48). The duration of hormone therapy use that was associated with an increased risk of ovarian cancer is unknown.[5]

5.3 Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal

women receiving estrogens has been reported.

5.4 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. Discontinue estrogens, including BIJUVA if hypercalcemia occurs, and take appropriate measures to reduce the serum calcium level.

5.5 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue BIJUVA pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Permanently discontinue estrogens, including BIJUVA, if examination reveals papilledema or retinal vascular lesions.

5.6 Elevated Blood Pressure

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

5.7 Exacerbation of Hypertriglyceridemia

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

5.8 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with hepatic impairment. Exercise caution in any woman with a history of cholestatic jaundice associated with past estrogen use or with pregnancy. In the case of recurrence of cholestatic jaundice, discontinue BIJUVA.

5.9 Exacerbation of Hypothyroidism

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

5.10 Fluid Retention

Estrogens plus progestogens may cause some degree of fluid retention. Monitor any woman with a condition(s) that might predispose her to fluid retention, such as cardiac or renal impairment. Discontinue estrogen plus progestogen therapy, including BIJUVA, with evidence of medically concerning fluid retention.

5.11 Hypocalcemia

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

5.12 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. Consider whether the benefits of estrogen therapy, including BIJUVA, outweigh the risks in such women.

5.13 Exacerbation of Other Conditions

Estrogen therapy, including BIJUVA, may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas. Consider whether the benefits of estrogen therapy outweigh the risks in women with such conditions.

5.14 Laboratory Tests

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

5.15 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), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.
- Impaired glucose tolerance.

6 ADVERSE REACTIONS

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

- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Malignant Neoplasms *[see Boxed Warning, 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 trial that included 1,835 postmenopausal women (1,684 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 either BIJUVA (estradiol and progesterone) capsules group and numerically greater than those reported in the placebo group are listed in Table 1.

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

Preferred Term	BIJUVA 0.5 mg/100 mg (N=424)	BIJUVA 1 mg/100 mg (N=415)	Placebo (N=151)
Breast tenderness	17 (4.0)	43 (10.4)	1 (0.7)
Headache	17 (4.0)	14 (3.4)	1 (0.7)
Nausea	15 (3.5)	9 (2.2)	1 (0.7)
Vaginal bleeding	10 (2.4)	14 (3.4)	0
Vaginal discharge	8 (1.9)	14 (3.4)	1 (0.7)
Pelvic pain	12 (2.8)	13 (3.1)	0

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of BIJUVA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders

Abdominal pain and discomfort, abdominal distention, diarrhea, nausea, vomiting.

General disorders and administration site conditions

Fatigue, feeling abnormal, malaise.

Investigations

Weight increased.

Metabolism and nutrition disorders

Fluid retention.

Musculoskeletal and connective tissue disorders

Muscle spasms, pain in extremity.

Nervous system disorders

Dizziness, headache, somnolence.

Psychiatric disorders

Insomnia, sleep disorder.

Reproductive system and breast disorders

Breast pain, breast tenderness, uterine bleeding.

Skin and subcutaneous tissue disorders

Night sweats, pruritus.

Vascular disorders

Hot flush.

7 DRUG INTERACTIONS

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 adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

BIJUVA is 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 (estrogens and progestins) before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

Estrogens plus progestogens 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. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BIJUVA and any potential adverse effects on the breastfed child from BIJUVA or from the underlying maternal condition.

8.4 Pediatric Use

BIJUVA is not indicated for use in pediatric patients. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing BIJUVA 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 trial (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)]*.

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 *[see Clinical Studies (14.5)]*.

It is unknown whether these findings apply to younger postmenopausal women *[see Clinical Studies (14.5)]*. The safety and efficacy of BIJUVA for the prevention of dementia has not been established.

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 therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

BIJUVA (estradiol and progesterone) is an oval shaped opaque capsule in which the estradiol is solubilized and the progesterone is micronized and suspended in the mixture of medium chain mono and di-glycerides and lauroyl polyoxyl-32 glycerides.

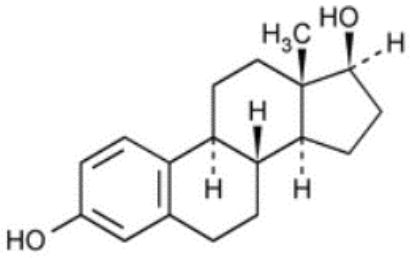
Each 0.5 mg/100 mg capsule is light pink on one side, dark pink on the other side, and printed with "5C1" in white ink.

Each 1 mg/100 mg capsule is light pink on one side, dark pink on the other side, and printed with "1C1" in white ink.

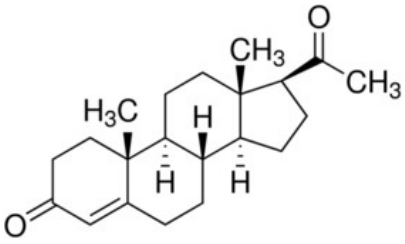
Estradiol (estra-1,3,5 (10)-triene-3,17β-diol), an estrogen, has a molecular weight of 272.38, and chemical formula $C_{18}H_{24}O_2$.

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 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 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

Generally, a serum estrogen concentration does not predict an individual woman's therapeutic response to BIJUVA nor her risk for adverse outcomes. Likewise, exposure comparisons across different estrogen products to infer efficacy or safety for the individual woman may not be valid.

12.3 Pharmacokinetics

Absorption

The oral absorption of both estradiol and progesterone is subject to first-pass metabolism. After multiple doses of BIJUVA (estradiol and progesterone) capsules administered with food, the t_{max} (the time at which the maximum concentration is attained) for estradiol is approximately 3 to 6 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. A dose-dependent increase in AUC_{0-t} and C_{max} of estradiol and a slightly more than proportionality increase in AUC_{0-t} and C_{max} of estrone were observed when the dose of estradiol was increased from 0.5 mg/day to 1 mg/day (Table 2).

Figure 1: Mean Steady-State Serum Estradiol Concentrations Following Daily Oral Administration of 0.5 mg Estradiol/100 mg Progesterone or 1 mg Estradiol/100 mg Progesterone with Food (Baseline Adjusted, at Day 7)

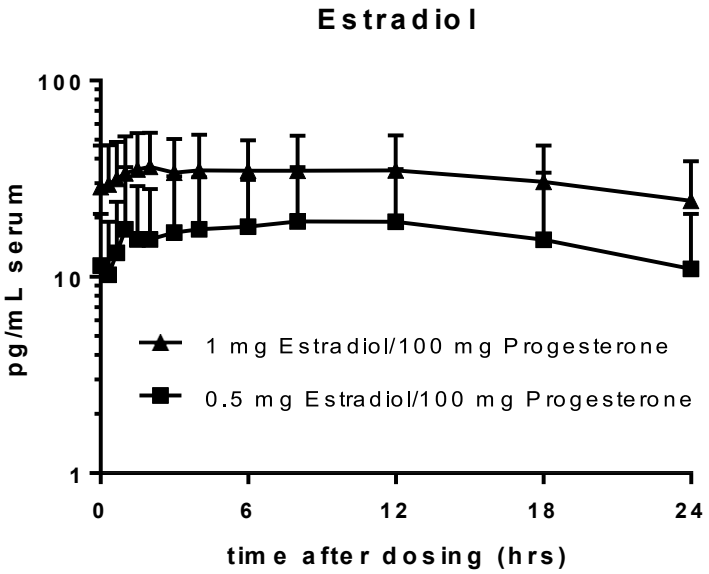


Figure 2: Mean Steady-State Serum Progesterone Concentrations Following Daily Oral Administration of 0.5 mg Estradiol/100 mg Progesterone or 1 mg Estradiol/100 mg Progesterone with Food (Baseline Adjusted, at Day 7)

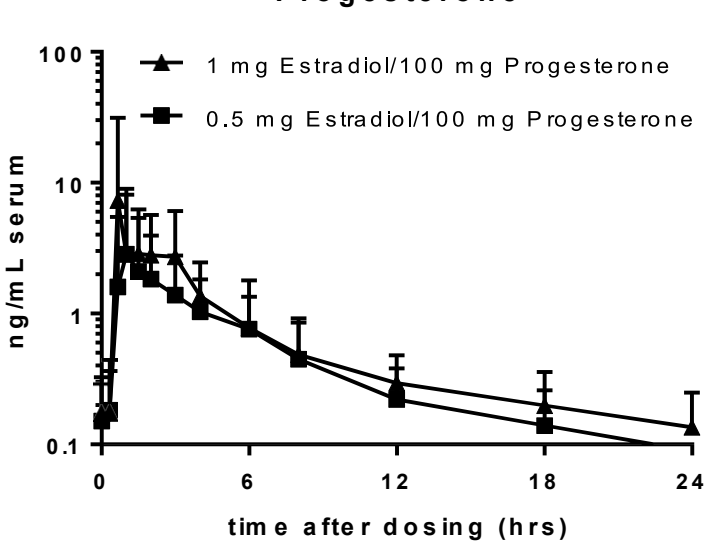


Table 2: Mean (SD) Steady-State Pharmacokinetic Parameters after Administration of Capsules Containing 0.5 mg Estradiol/100 mg Progesterone or 1 mg Estradiol/100 mg Progesterone with Food in Healthy Postmenopausal Women (Baseline Adjusted, at Day 7)

Dosage Strength (estradiol/progesterone)	BIJUVA 0.5 mg/100 mg Mean (SD)		BIJUVA 1 mg/100 mg Mean (SD)	
Estradiol	**N**		**N**	
$AUC_{0-\tau}$ (pg·h/mL)	17	386.8 (356.6)	20	772.4 (384.1)
C_{max} (pg/mL)	17	23.95 (16.86)	20	42.27 (18.60)
C_{avg} (pg/mL)	17	16.64 (14.50)	19	33.99 (14.53)
t_{max} (h)[#]	17	6.00 (0.00 – 12.00)	19	3.00 (0.67 – 18.03)
$t_{½}$ (h)*	11	28.01 (9.99)	19	26.47 (14.61)
Estrone				
$AUC_{0-\tau}$ (pg·h/mL)	17	1981 (976.0)	20	4594 (2138)
C_{max} (pg/mL)	17	108.0 (48.58)	20	238.5 (100.4)
C_{avg} (pg/mL)	17	82.81 (40.80)	20	192.1 (89.43)
t_{max} (h)[#]	17	11.98 (2.00 – 18.00)	20	5.00 (1.50 – 12.00)
$t_{½}$ (h)*	17	20.46 (5.61)	19	22.37 (7.64)
Progesterone				
$AUC_{0-\tau}$ (ng·h/mL)	17	12.19 (11.01)	20	18.05 (15.58)

C_{max} (ng/mL)	17	4.40 (5.72)	20	11.31 (23.10)
C_{avg} (ng/mL)	17	0.55 (0.45)	20	0.76 (0.65)
t_{max} (h)[#]	17	2.00 (0.67 – 8.00)	20	2.51 (0.67 – 6.00)
$t_{½}$ (h)	13	8.77 (2.78)	18	9.98 (2.57)

Median and range
*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 and the median t_{max} of progesterone was delayed from 2 hours to 3 hours. Concomitant food ingestion had no effect on the AUC of the estradiol component of BIJUVA but decreased C_{max} by approximately 54% and delayed median t_{max} from 1 hour to 12 hours.

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, 0.5 mg/100 mg or 1 mg/100 mg, the half-life of estradiol was 28 ± 10 hours and 26 ± 15 hours, respectively, and the half-life of progesterone was 9 ± 3 hours and 10 ± 3 hours, respectively (Table 2).

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 intestine followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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 in Postmenopausal Women

The effectiveness and safety of BIJUVA (estradiol and progesterone) capsules, 0.5 mg/100 mg and 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 149 women received BIJUVA (estradiol and progesterone) capsules, 0.5 mg/100 mg, 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 and 2) mean weekly reduction in severity of moderate to severe vasomotor symptoms with BIJUVA compared to placebo at Weeks 4 and 12.

Overall, BIJUVA (estradiol and progesterone) capsules, 0.5 mg/100 mg and 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. 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 0.5 mg/100 mg (N=149)	**BIJUVA 1 mg/100 mg (N=141)**	**Placebo (N=135)**
Week 4	n=144	n=134	n=126
Baseline	72.3 (28.06)	72.1 (27.80)	72.3 (23.44)
Mean (SD) change from baseline	-35.1 (29.14)	-40.6 (30.59)	-26.4 (27.05)
Difference from placebo*	-8.07 (3.25)	-12.81 (3.30)	---
P-value**	0.013	< 0.001	---
Week 12	n=129	n=124	n=115
Baseline	72.8 (28.96)	72.2 (25.04)	72.2 (22.66)
Mean (SD) change from baseline	-53.7 (31.93)	-55.1 (31.36)	-40.2 (29.79)
Difference from placebo*	-15.07 (3.39)	-16.58 (3.44)	---
P-value**	<0.001	<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 0.5 mg/100 mg (N=149)	**BIJUVA 1 mg/100 mg (N=141)**	**Placebo (N=135)**
Week 4	n=144	n=134	n=126
Baseline	2.51 (0.248)	2.54 (0.325)	2.52 (0.249)
Mean (SD) change from baseline	-0.51 (0.563)	-0.48 (0.547)	-0.34 (0.386)
Difference from placebo*	-0.17 (0.060)	-0.13 (0.061)	---
P-value**	0.005	0.031	---
Week 12	n=129	n=124	n=115
Baseline	2.51 (0.248)	2.55 (0.235)	2.52 (0.245)
Mean (SD) change from baseline	-0.90 (0.783)	-1.12 (0.963)	-0.56 (0.603)
Difference from placebo*	-0.39 (0.099)	-0.57 (0.100)	---
P-value**	<0.001	<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, 0.5 mg/100 mg or 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 in Postmenopausal Women

Effects of BIJUVA (estradiol and progesterone) capsules, 0.5 mg/100 mg and 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, 0.5 mg/100 mg or 1 mg/100 mg, and had baseline and post-baseline endometrial biopsies. During the trial, endometrial biopsy assessments revealed one (1) case of endometrial hyperplasia and no cases of endometrial cancer in women who received BIJUVA (estradiol and progesterone) 0.5 mg/100 mg capsules, one (1) case of endometrial hyperplasia and no cases of endometrial cancer in women who received BIJUVA (estradiol and progesterone) 1 mg/100 mg capsules, and no cases of endometrial 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 0.5 mg/100 mg (N=303)	BIJUVA 1 mg/100 mg (N=281)	Placebo (N=92)
Hyperplasia incidence rate % (n/N)	1/303 (0.33)	1/281 (0.36)	0/92 (0.00)
One-sided upper 95% confidence limit	1.83	1.97	3.93

Six (6) cases of disordered proliferative endometrium were reported for BIJUVA (estradiol and progesterone) capsules, 0.5 mg/100 mg, and 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 in Postmenopausal Women

Uterine bleeding or spotting was evaluated in the 52-week safety study by daily diary. At 52 weeks, cumulative amenorrhea was reported by 67.6% of women who received BIJUVA (estradiol and progesterone) capsules, 0.5 mg/100 mg, 56.1% of women who received BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, and 78.9% who received placebo.

14.4 Women's Health Initiative Estrogen Plus Progestin Trial

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

The WHI estrogen plus progestin trial was stopped early. After an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer crossed the predefined stopping threshold. The global index was supportive of a finding of overall harm. The absolute excess risk of events included in the global index was 19 per 10,000 women-years.

Results of the trial, which enrolled 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.[6,7]

Table 6: Relative Risk and Risk Difference Observed in the WHI Estrogen Plus Progestin Trial at an Average of 5.6 Years [a,b]

Event	Relative Ratio (95% CI) [c]	Risk Difference (CEMPA vs placebo/10,000 WYs)
CHD events	1.18 (0.95-1.45)	6 (41 vs 35)
Non-fatal MI	*1.24 (0.98-1.56)*	*6 (35 vs 29)*
CHD death	*1.05 (0.76-1.45)*	*1 (16 vs 15)*

All Strokes	1.37 (1.07-1.76)	9 (33 vs 24)
Deep vein thrombosis[d]	1.87 (1.37-2.54)	12 (25 vs 14)
Pulmonary embolism	1.98 (1.36-2.87)	9 (18 vs 9)
Invasive breast cancer[e]	1.24 (1.01-1.53)	9 (43 vs 35)
Colorectal cancer	0.62 (0.43-0.89)	-6 (10 vs 17)
Endometrial cancer[d]	0.83 (0.49-1.40)	-1 (6 vs 7)
Hip fracture	0.67 (0.47-0.95)	-6 (11 vs 17)
Vertebral fracture[d]	0.68 (0.48-0.96)	-6 (12 vs 17)
Total factures[d]	0.76 (0.69-0.83)	-51 (161 vs 212)
Overall mortality[c,f]	0.97 (0.81-1.16)	-1 (52 vs 53)
Global Index[g]	1.12 (1.02-1.24)	20 (189 vs 168)

[a] Adapted from 2013 WHI substudy (CE/MPA n=8,506, placebo n=8,102). WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Results are based on centrally adjudicated data
[c] In the WHI studies, hazard ratios were estimated using Cox proportional hazards models comparing treatment to placebo; however, they are described here as relative risks. Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[d] Not included in "global index."
[e] Includes metastatic and non-metastatic breast cancer with the exception of in situ cancer.
[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
[g] A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, PE, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The results of the WHI estrogen plus progestin trial in women 50-59 years of age (N=2,837 for CE/MPA; N=2,683 for placebo) are shown in Table 7.

Table 7: Relative Risk and Risk Difference Observed Among Women 50-59 Years of Age in the WHI Estrogen Plus Progestin Trial at an Average of 5.8 Years[a,b]

Event	**Relative Ratio (95% CI) [c]**	**Risk Difference (CEMPA vs placebo/10,000 WYs)**
CHD events	1.34 (0.82-2.19)	5 (23 vs 17)
Non-fatal MI	*1.32 (0.77-2.25)*	*4 (19 vs 15)*
CHD death	*0.77 (0.33-1.79)*	*-2 (6 vs 8)*
All Strokes	1.51 (0.81-2.82)	5 (15 vs 10)
Deep vein thrombosis[d]	3.01 (1.36-6.66)	10 (15 vs 5)
Pulmonary embolism	2.05 (0.89-4.71)	6 (11 vs 5)
Invasive breast cancer[e]	1.21 (0.81-1.80)	6 (33 vs 27)
Colorectal cancer	0.79 (0.29-2.18)	-1 (4 vs 5)
Endometrial cancer[d]	1.07 (0.33-3.53)	0 (4 vs 3)

Hip fracture	0.17 (0.22-1.45)	-3 (1 vs 3)
Vertebral fracture[d]	0.38 (0.15-0.97)	-6 (4 vs 10)
Total factures[d]	0.82 (0.68-1.00)	-25 (120 vs 145)
Overall mortality[c,f]	0.67 (0.43-1.04)	-10 (21 vs 31)
Global Index[g]	1.12 (0.89-1.40)	12 (103 vs 91)

[a] Adapted from 2013 WHI trial (CE/MPA n=2,837; placebo=2,683). WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Results are based on centrally adjudicated data.
[c] In the WHI studies, hazard ratios were estimated using Cox proportional hazards models comparing treatment to placebo; however, they are described here as relative risks. Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[d] Not included in "global index."
[e] Includes metastatic and non-metastatic breast cancer with the exception of in situ cancer.
[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
[g] A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, PE, colorectal cancer, hip fracture, or death due to other causes.

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 effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD), and mixed 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.

After an average follow-up of 4 years, the relative risk of probable dementia for CE/MPA versus placebo was 2.01 (95% CI, 1.19 to -3.42), with a risk difference of 23 per 10,000 WYs (46 versus 23). 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 Use in Specific Populations (8.5)]*.[8]

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BIJUVA (estradiol and progesterone) capsules, 0.5 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 (5C1). BIJUVA (estradiol and progesterone) capsules, 0.5 mg/100 mg, are provided in a blister package of 30 capsules.

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, 0.5 mg/100 mg	NDC 68308-751-30
BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg	NDC 68308-750-30

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]

17 PATIENT COUNSELING INFORMATION

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

Vaginal Bleeding

Inform postmenopausal women to report any vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.2)]*.

Possible Serious Adverse Reactions with Estrogen Plus Progestogen Therapy

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

Possible Common Adverse Reactions with Estrogen Plus Progestogen Therapy

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

Missed Evening Dose of BIJUVA

Advise the woman 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.

PATIENT INFORMATION

BIJUVA® (bī joo' vah)

(estradiol and progesterone)

capsules, for oral use

What is the most important information I should know about BIJUVA (a combination of estrogen and progestogen)?

- Do not use estrogens with or without progestogens to prevent heart disease, heart attacks, strokes, or dementia (decline of brain function).
- Using estrogens with progestogens may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.

What is BIJUVA?

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

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 intense 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 use BIJUVA?

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

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

Do not start using 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.
- **have been diagnosed with a bleeding disorder.**
- **currently have or have had certain cancers.**
  Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus (womb). If you have or have had cancer, talk with your healthcare provider about whether you should use BIJUVA.
- **currently have or have had blood clots.**
- **had a stroke or heart attack.**
- **currently have or have had liver problems.**
- **are allergic to BIJUVA or any of its ingredients.** See the list of ingredients in BIJUVA at the end of this leaflet.

Before you use 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 any other medical conditions that may become worse while you are using BIJUVA.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as:
  - asthma (wheezing)
  - diabetes
  - a genetic problem called porphyria
  - lupus
  - hypertension (high blood pressure)
  - have high calcium in your blood
  - epilepsy (seizures)
  - migraine
  - 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 using 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. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get new medicine.

How should I use 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
- high blood pressure
- high levels of fat in your blood (triglycerides)
- liver problems
- changes in thyroid hormone levels
- swelling or fluid retention
- cancer changes of endometriosis
- enlargement of benign tumors of the uterus (“fibroids”)

- gallbladder disease
- high or low blood calcium levels
- changes in vision
- 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

Common side effects of BIJUVA include:

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

Tell your healthcare provider if you have any side effects that bother you or do 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 Mayne Pharma at 1-844-825-8500.

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 using BIJUVA.
- If you have a uterus, talk with your healthcare provider about whether BIJUVA is right for you.
- In general, the addition of a progestogen is recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb).
- See your healthcare provider right away if you get vaginal bleeding while using 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 ingredients: 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.

For information, call Mayne Pharma at 1-844-825-8500.

Distributed by:
Mayne Pharma
Raleigh, NC 27609

Revised 2/2026

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