PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrBIJUVA™

Estradiol and Progesterone capsule

Capsules, 0.5 mg estradiol (as estradiol hemihydrate)/100 mg progesterone and

1 mg estradiol (as estradiol hemihydrate)/100 mg progesterone, oral

Estrogen / Progestogen

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BIJUVA (estradiol and progesterone capsule) is indicated for:

- Treatment of moderate to severe vasomotor symptoms associated with menopause in women with intact uterus.

BIJUVA is recommended for use only in patients with an intact uterus since the regimen includes a progestogen whose role is to assist in the prevention of endometrial hyperplasia.

1.1 Pediatrics

Pediatrics (<18 years of age): BIJUVA is not indicated for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): BIJUVA has not been studied in women over 65 years old; therefore, BIJUVA is not recommended in women over 65 years of age.

2 CONTRAINDICATIONS

BIJUVA is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **Dosage Forms, Strengths, Composition and Packaging**.
- Patients with liver dysfunction or disease as long as liver function tests have failed to return to normal
- Patients with known, suspected, or personal history of estrogen-dependent or progestin-dependent malignant neoplasia (e.g., breast cancer or endometrial cancer)
- Patients with endometrial hyperplasia
- Patients with undiagnosed abnormal genital bleeding
- Patients with known or suspected pregnancy
- Patients who are breastfeeding
- Patients with active or past history of arterial thromboembolic disease (e.g., stroke, myocardial infarction, coronary heart disease)
- Patients with classical migraine
- Patients with active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis
- Partial or complete loss of vision due to ophthalmic vascular disease

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n = 16 608) and oral *estrogen-alone* therapy (n = 10 739) in postmenopausal women aged 50 to 79 years. [1-3]

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increase risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.[1]

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.[2]

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the approved indication.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

BIJUVA is a continuous combined Hormone Replacement Therapy (HRT) intended for use in women with intact uteri.

BIJUVA should be used at the lowest effective dose and for a duration consistent with treatment goals and the benefits and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

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[1] Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002; 288(3):321-333.

[2] The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative randomized controlled trial. JAMA. 2004; 291(14):1701 – 1712.

[3] Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. The Women's Health Initiative randomized trial. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. JAMA. 2003; 289(24):32433253.

4.2 Recommended Dose and Dosage Adjustment

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

BIJUVA has not been studied in women over 65 years old; therefore, BIJUVA is not recommended in women over 65 years of age.

BIJUVA is not indicated for pediatric use.

4.3 Missed Dose

BIJUVA should be taken as soon as possible after missing a dose. However, the missed dose should be skipped if it is almost time to take the next dose. Patients should be advised not to double the dose. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

5 OVERDOSAGE

Symptoms of Overdose
Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Progestin overdosage has been characterized by depressed mood, tiredness, acne, and hirsutism.

Treatment of Overdose
In the event of a possible overdose, the physician should observe the patient closely and symptomatic treatment should be given.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Oral	Softgel Capsule • 1 mg estradiol (as estradiol hemihydrate) and 100 mg progesterone • 0.5 mg estradiol (as estradiol hemihydrate) and 100 mg progesterone	FD&C Red #40, gelatin, glycerin, hydrolyzed gelatin, lauryl polyoxyl-32 glycerides, lecithin, medium chain mono and di-glycerides, medium chain triglycerides, pharmaceutical ink, purified water, and titanium dioxide

BIJUVA 0.5 mg estradiol/100 mg progesterone: oval shaped opaque softgel capsules, light pink on one side and dark pink on the other side, printed with “5C1” in white ink.

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

Both strengths of BIJUVA (estradiol and progesterone) capsules are provided in a blister package of 30 capsules or samples of 5 capsules.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

CARCINOGENESIS AND MUTAGENESIS

Breast Cancer
In a one-year trial, among 1,835 women who received a combination of estradiol plus progesterone or placebo, six new cases of breast cancer were diagnosed. Two (2) cases in the 1 mg estradiol/100 mg progesterone treatment arm [N=415], 2 cases in the 0.5 mg estradiol/100 mg progesterone treatment arm [N=424], 1 case in the 0.5 mg estradiol/50 mg progesterone treatment arm [N=421], and 1 case in the 0.25 mg estradiol/50 mg progesterone treatment arm [N=424]). No new cases of breast cancer were diagnosed in the placebo group [N=151].

Available epidemiological data indicate that the use of combined *estrogen plus progestin* by postmenopausal women is associated with an increased risk of invasive breast cancer.

In the *estrogen plus progestin* arm of the WHI trial, among 10 000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined Hormone Replacement Therapy [HRT] versus 30 on placebo).[1]

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean (SD) 1.7 cm (1.1) vs 1.5 cm (0.9), respectively; P = 0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.[3]

In the *estrogen-alone arm* of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.[2]

It is recommended that estrogens with or without progestins not be given to women with existing breast cancer or those with a previous history of the disease (see **CONTRAINDICATIONS**).

There is a need for caution in prescribing estrogens with or without progestins for women with known risk factors associated with the development of breast cancer, such as strong family history

of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/or atypical hyperplasia at breast biopsy). Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of Hormone Replacement Therapy (HRT) treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

Estrogen-progestogen combined treatment may increase the density of breast tissue, potentially adversely affecting the capability of mammography to detect breast cancer.

The overall benefits and possible risks of HRT should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counselling.

Endometrial Hyperplasia and Endometrial Carcinoma
The use of unopposed estrogen by women with intact uteri increases the risk of endometrial hyperplasia and endometrial carcinoma. Estrogen should be prescribed with an appropriate dosage of a progestin in women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1 percent or less with BIJUVA capsules, 1 mg/100 mg and 0.5 mg/100 mg.

All women taking estrogen/progestin combination should undergo clinical surveillance for endometrial abnormalities. Adequate diagnostic measures, including endometrial sampling, should be performed in all cases of undiagnosed persistent or recurring abnormal genital bleeding.

Ovarian Cancer
Some recent epidemiologic studies have found that the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

CARDIOVASCULAR

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.[1, 4,]

[4] Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA. 1998; 280(7):605-613.

[5]The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women.[1, 2]

WHI Trial Findings
In the combined *estrogen plus progestin* arm of the WHI trial, among 10 000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo).[1]

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10 000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on estrogen-alone therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD.[2]

HERS and HERS II Findings
In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n = 2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE 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 hormone-treated group than in the placebo group in year 1, but not during the subsequent years.[4]

From the original HERS trial, 2 321 women consented to participate in an open label extension of HERS, known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.[5]

Blood Pressure
Women using HRT sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

EAR/NOSE/THROAT

Otosclerosis
Estrogens should be used with caution in patients with otosclerosis.

ENDOCRINE AND METABOLISM

[5] Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA. 2002; 288(1):49-57.

Glucose and Lipid Metabolism
A worsening of glucose tolerance and lipid metabolism has been observed in a significant percentage of peri- and postmenopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

Women with familial hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started. BIJUVA may increase serum triglyceride levels (see ADVERSE REACTIONS). Women with pre-existing hypertriglyceridemia should be followed closely during hormone replacement therapy. HRT in these women may be associated with a further increase in triglyceride levels bearing the risk of pancreatitis. In a 1-year clinical trial, 2 cases of acute pancreatitis were reported; 1 each in the 1 mg estradiol/100 mg progesterone [N=415] and 0.5 mg estradiol/50 mg progesterone [N=421] treatment arms (see ADVERSE REACTIONS). BUJUVA has not been studied in women with triglyceride levels >300 mg/dL (>3.4 mmol/L).

Heme Metabolism
Women with porphyria need special surveillance.

Calcium and Phosphorus Metabolism
Because the prolonged use of estrogens with or without progestins influences the metabolism of calcium and phosphorus, estrogens with or without progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Hypothyroidism
Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see **Drug-Laboratory Test Interactions**).

GENITOURINARY

Vaginal Bleeding
Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt diagnostic measures like hysteroscopy, endometrial biopsy, or curettage to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Uterine Leiomyomata
Pre-existing uterine leiomyoma may increase in size during estrogen use. Growth, pain, or tenderness of uterine leiomyoma requires discontinuation of medication and appropriate investigation.

Endometriosis
Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

HEMATOLOGIC

Venous Thromboembolism

Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10 000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.[1]

In the *estrogen-alone* arm of the WHI trial, among 10 000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.[2]

In a one-year trial, among 1,835 women who received a combination of estradiol plus progesterone or placebo, one case of deep vein thrombosis was diagnosed in the 0.5 mg estradiol/50 mg progesterone treatment group.

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index >30 kg/m^2), and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery, or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens with or without progestins should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

HEPATIC/BILIARY/PANCREATIC

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

Hepatic hemangioma
Particular caution is indicated in women with hepatic hemangiomas as estrogens may cause an exacerbation of this condition.

Jaundice
Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued, and appropriate investigations carried out.

Liver Function Tests
Liver function tests should be done periodically in subjects who are suspected of having hepatic

disease. For information on endocrine and liver function tests, see the section under **Monitoring and Laboratory Tests.**

IMMUNE

Angioedema
Estrogen may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

Systemic Lupus Erythematosus
Particular caution is indicated in women with systemic lupus erythematosus, as HRT may cause an exacerbation of this condition.

MONITORING AND LABORATORY TESTS

Before BIJUVA is administered, the patient should have a complete physical examination, including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done when indicated. Baseline tests should include mammography, measurement of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3 to 6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals of at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

The importance of regular self-examination of the breasts should be discussed with the patient.

NEUROLOGIC

Cerebrovascular Insufficiency
Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis, or loss of consciousness should discontinue medication.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be re-evaluated.

Dementia
Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women aged 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical sub-study of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (*estrogen plus progestin or estrogen-alone*) reduces the risk of dementia in women aged 65 (age range 65-79

years) and over and free of dementia at baseline.[6,7]

In the *estrogen plus progestin* arm of the WHIMS (n = 4 532), women with an intact uterus were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10 000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo).[6]

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10 000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on estrogen-alone versus 25 on placebo), although this difference did not reach statistical significance.[7]

When data from the *estrogen plus progestin* arm of the WHIMS and the *estrogen-alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10 000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on *estrogen plus progestin* or *estrogen-alone* versus 23 on placebo).[7]

Epilepsy
Particular caution is indicated in women with epilepsy, as estrogens with or without progestins may cause an exacerbation of this condition.

RENAL

Fluid Retention
Estrogens with or without progestins may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

7.1 Special Populations

7.1.1 Pregnant Women

BIJUVA must not be used by women who are or may be pregnant (see **CONTRAINDICATIONS**). If pregnancy occurs during medication with BIJUVA, treatment must be discontinued immediately.

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[6] Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: A randomized controlled trial. JAMA. 2003; 289(20):2651-2662.

[7] Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. Women's Health Initiative Memory Study. JAMA. 2004; 291(24):2947-2958.

7.1.2 Breast-feeding

BIJUVA must not be used by women who are lactating and breast-feeding (see **CONTRAINDICATIONS**).

7.1.3 Pediatrics

Pediatrics (<18 years of age): BIJUVA is not indicated for pediatric use.

7.1.4 Geriatrics

Geriatrics (>65 years of age): BIJUVA has not been studied in women over 65 years old; therefore, BIJUVA is not recommended in women over 65 years of age. The use of combined *estrogen plus progestin* in women aged 65 and over may increase the risk of developing probable dementia (see **WARNINGS AND PRECAUTIONS, Neurologic**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

See **WARNINGS AND PRECAUTIONS** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combinations in general:

Blood and Lymphatic System Disorders: Altered coagulation tests (see **DRUG INTERACTIONS, Drug-Laboratory Test Interactions**).

Cardiac Disorders: Palpitations; increase in blood pressure (see **WARNINGS AND PRECAUTIONS**); coronary thrombosis

Endocrine disorders: Increased blood sugar levels; decreased glucose tolerance.

Eye disorders: Intolerance to contact lenses; neuro-ocular lesions (e.g., retinal thrombosis, optic neuritis); steepening of the corneal curvature; visual disturbances.

Gastrointestinal disorders: Abdominal discomfort (cramps, pressure, pain, bloating); nausea; vomiting.

General disorders and administration site conditions: Anorexia; changes in appetite; changes in body weight; fatigue; change in libido.

Hepatobiliary disorders: Asymptomatic impaired liver function; cholestatic jaundice; gallbladder disorder.

Musculoskeletal and connective tissue disorders: Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

Nervous system disorders: Aggravation of migraine episodes; dizziness; headaches; neuritis.

Psychiatric disorders: Irritability; mental depression; nervousness.

Renal and urinary disorders: Cystitis; dysuria; edema; sodium retention.

Reproductive system and breast disorders: Breakthrough bleeding; breast swelling, tenderness; changes in cervical erosion and amount of cervical secretion; change in menstrual flow; dysmenorrhea; dyspareunia; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; spotting; vaginal itching/discharge.

Skin and subcutaneous tissue disorders: Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; hirsutism and acne; itching; loss of scalp hair.

Vascular disorders: Isolated cases of thromboembolic disorders; thrombophlebitis.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of BIJUVA (estradiol and progesterone) was assessed in a 1-year, randomized, double-blind, placebo-controlled pivotal clinical trial that included 1,835 postmenopausal women. In this study, 151 women received placebo, 415 women received 1 mg E2/100 mg P; 424 women received 0.5 mg E2/100 mg P; 421 women received 0.5 mg E2/50 mg P and 424 women received 0.25 mg E2/50 mg P. Most women (~70%) in the active treatment groups were treated for ≥ 326 days.

Overall, the most common TEAE (regardless of causality) across combined active treatment groups was headache (8.5%), followed by nasopharyngitis (7.5%), breast tenderness (5.9%), upper respiratory tract infection (5.8%), nausea (4.8%), back pain (3.7%), abdominal pain (3.6%), sinusitis (3.6%), and dizziness (3.0%); all common TEAEs occurred more frequently in the active treatments group as compared to placebo.

Table 2 shows the Treatment Emergent Adverse Events (TEAE) reported in the pivotal study at a frequency of ≥ 1%, and related to treatment, in women receiving BIJUVA administered at a dose of 1 mg estradiol/100 mg progesterone and 0.5 mg estradiol/100 mg progesterone at a frequency higher than for the control group. Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA).

Table 2. Treatment-Emergent Adverse Reactions Reported at a Frequency of ≥ 1%, Treatment Related and Numerically More Common in Women Receiving BIJUVA at a dose of 1 mg Estradiol/100 mg Progesterone or 0.5 mg Estradiol/100 mg Progesterone

System Organ Class MedDRA Preferred Term	BIJUVA 1 mg E2/100 mg P N= 415 n (%)	BIJUVA 0.5 mg E2/100 mg P N = 424 n (%)	PLACEBO n = 151 n (%)
GASTROINTESTINAL DISORDERS			
Nausea	9 (2.2)	15 (3.5)	1 (0.7)
Abdominal pain	9 (2.2)	6 (1.4)	1 (0.7)
Abdominal distension	9 (2.2)	3 (0.7)	0
Abdominal pain upper	4 (1.0)	3 (0.7)	1 (0.7)
Abdominal pain lower	4 (1.0)	1 (0.2)	1 (0.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue	6 (1.4)	3 (0.7)	1 (0.7)
INFECTIONS AND INFESTATIONS			
Vulvovaginal mycotic infection	4 (1.0)	6 (1.4)	3 (2.0)
INVESTIGATIONS			
Weight increased	7 (1.7)	6 (1.4)	2 (1.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Back pain	5 (1.2)	1 (0.2)	0 (0.0)
NERVOUS SYSTEM DISORDERS			
Headache	14 (3.4)	17 (4.0)	1 (0.7)
Dizziness	10 (2.4)	7 (1.7)	0 (0.0)
PSYCHIATRIC DISORDERS			
Irritability	4 (1.0)	3 (0.7)	2 (1.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Breast tenderness	43 (10.4)	17 (4.0)	1 (0.7)
Pelvic pain	13 (3.1)	12 (2.8)	0 (0.0)
Vaginal haemorrhage	14 (3.4)	10 (2.4)	0 (0.0)
Vaginal discharge	14 (3.4)	8 (1.9)	1 (0.7)
Breast pain	8 (1.9)	2 (0.5)	0 (0.0)
Uterine spasm	7 (1.7)	4 (0.9)	0 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia	6 (1.4)	6 (1.4)	0 (0.0)
Acne	6 (1.4)	4 (0.9)	0 (0.0)

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse events were reported in the pivotal clinical trial as related to treatment and in at least 1 patient. Adverse drug reactions are presented by MedDRA System Organ Class in order by preferred term.

Blood and lymphatic system disorders: Anemia, leukopenia, neutropenia.

Cardiac disorders: Atrioventricular block first degree, palpitations, stress cardiomyopathy,

unstable angina.

Ear and Labyrinth disorders: Ear swelling, vertigo.

Endocrine disorders: Hirsutism.

Eye disorders: Dry eye, vision blurred, visual impairment, vitreous floaters.

Gastrointestinal disorders: Abdominal discomfort, abdominal tenderness, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, faecal incontinence, flatulence, gastrointestinal pain, gastroesophageal reflux disease, oral discomfort, pancreatitis acute, vomiting.

General Disorders and Administration Site Conditions: Asthenia, axillary pain, chest discomfort, chest pain, chills, general oedema, malaise, night sweats, oedema peripheral.

Hepatobiliary disorders: Cholelithiasis.

Immune system disorders: Hypersensitivity.

Infections and Infestations: Bacterial vaginosis, erysipelas, folliculitis, furuncle, gastroenteritis, otitis media acute, skin candida, vaginal infection, urinary tract infection, vulvovaginal candidiasis.

Injury, Poisoning and Procedural Complications: Overdose, procedural pain.

Investigations: Activated partial thromboplastin time prolonged, alanine aminotransferase increased, antithrombin III decreased, antithrombin III increased, aspartate aminotransferase increased, biopsy endometrium abnormal, blood alkaline phosphatase increased, blood cholesterol increased, blood creatinine increased, blood fibrinogen decreased, blood fibrinogen increased, blood glucose increased, blood pressure abnormal, blood pressure increased, blood pressure diastolic increased, blood pressure systolic increased, blood triglycerides increased, hepatic enzyme increased, International normalized ration increased, lipids increased, liver function test abnormal, low density lipoprotein increased, protein C decreased, protein C increased, protein S decreased, protein S increased, protein urine present, prothrombin time prolonged, smear cervix abnormal, weight decreased.

Metabolism and Nutrition disorders: Decreased appetite, fluid retention, hyperlipidaemia, hyperphagia, hypertriglyceridaemia, hyperuricaemia, increased appetite.

Musculoskeletal and Connective Tissue Disorders: Arthralgia, arthritis, chest wall mass, fibromyalgia, joint swelling, limb discomfort, muscle spasms, myalgia, muscle twitching, pain in extremity, pain in jaw.

Neoplasm benign, malignant and unspecified: Adnexa uteri cyst, breast cancer female, invasive ductal breast carcinoma.

Nervous System Disorders: Aura, depressed level of consciousness, disturbance in attention, dysarthria, formication, hypoaesthesia, lethargy, memory impairment, migraine, migraine with aura, neuropathy peripheral, paraesthesia, parosmia, sciatica, somnolence, syncope, tension headache.

Psychiatric Disorders: Abnormal dreams, agitation, anxiety, anxiety disorder, depressed mood, depression, emotional distress, insomnia, libido increased, mood swings, sleep disorder, tearfulness.

Renal and urinary disorders: Polyuria, urine odour abnormal.

Reproductive System and Breast Disorders: Adnexa uteri pain, atrophic vulvovaginitis, benign breast neoplasm, breast calcifications, breast discharge, breast discomfort, breast enlargement , breast swelling, breast mass, breast cyst, cervical dysplasia, cervical polyp, cervix haemorrhage uterine, coital bleeding, dysmenorrhea, endometrial hypertrophy, fibrocystic breast disease, hot flush, metrorrhagia, nipple disorder, nipple exudate bloody, nipple pain, ovarian cyst, postmenopausal haemorrhage, uterine haemorrhage, uterine leiomyoma, uterine polyp, vulvovaginal pain, vulvovaginal pruritus.

Skin and Subcutaneous Tissue Disorders: acne cystic, dermal cyst, dry skin, erythema, hyperhidrosis, oedema mouth, onychoclasis, pruritus, pruritus generalized, rash, rash pruritic, skin hyperpigmentation, skin hypertrophy, skin warm, telangiectasia, urticaria.

Vascular disorders: Deep vein thrombosis, hypertension, thrombophlebitis superficial.

If adverse symptoms persist, the prescription of HRT should be re-considered.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The following adverse reactions that were potentially clinically significant were observed in the pivotal clinical trial: increase in triglyceride and AST/ALT laboratory values.

9 DRUG INTERACTIONS

9.1 Overview

Estrogens may diminish the effectiveness of anticoagulants, antidiabetic and antihypertensive agents. Preparations inducing liver enzymes (e.g., barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone, or rifampicin) may interfere with the activity of orally administered estrogens.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP 3A4). Therefore, inducers or inhibitors of CYP 3A4 may affect estrogen drug metabolism. Inducers of CYP 3A4 such as St. John's Wort (*Hypericum perforatum*) preparations, anticonvulsants (e.g. phenobarbital, phenytoin, oxcarbazepine, topiramate) and anti-infectives (e.g. rifampin, rifabutin) may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in uterine bleeding profile.

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, fluconazole, itraconazole), verapamil, macrolides (e.g., erythromycin, clarithromycin), diltiazem and grapefruit juice, can increase plasma concentrations of the estrogen or the progesterone or both, possibly resulting in side effects.

When co-administered with sex hormones, many anti-HIV protease inhibitors (e.g., nelfinavir, ritonavir, ritonavir-boosted protease inhibitors), HCV protease inhibitors (e.g., boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine, efavirenz) can increase or decrease plasma concentrations of estrogen or progestin or both. These changes may alter the safety and effectiveness of BIJUVA. Healthcare providers should refer to the label of the individual anti-HIV/HCV protease inhibitor or non-nucleoside reverse transcriptase inhibitor for further drug-drug interaction information.

One in vitro study has shown cytochrome P450 1A2 (CYP 1A2) to be partially involved in the metabolism of 17β-estradiol through hydroxylation. The clinical significance of CYP 1A2 metabolism is unknown.

9.2 Drug-Drug Interactions

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

9.3 Drug-Food Interactions

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. (see **DOSAGE AND ADMINISTRATION SECTION)**.

Inhibitors of CYP 3A4 such as grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

9.4 Drug-Herb Interactions

It was found that some herbal products (e.g., St. John's wort) which are available as over the counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be made aware of the other non-prescription products concomitantly used by the patient, including herbal and natural products obtained from the widely spread health stores.

9.5 Drug-Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; decreased antithrombin III; increased norepinephrine-induced platelet aggregability;
- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T_4) as measured by column or radioimmunoassay; free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered

- other binding proteins may be elevated in serum, e.g., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively; free or biologically active hormone concentrations are unchanged (see **ACTION AND CLINICAL PHARMACOLOGY**)
- impaired glucose tolerance
- reduced serum folate concentration
- increased serum triglyceride and phospholipid concentration

The following laboratory results may be altered by the use of progesterone: levels of gonadotropin, plasma progesterone, and urinary pregnanediol.

In clinical trials with BIJUVA, there have been no known effects on fibrinogen, antithrombin III, or protein C system (protein C/S).

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks. The pathologist should be informed that the patient is receiving estrogen/progestin therapy when relevant specimens are submitted.

9.6 Drug-Lifestyle Interactions

The effect of lifestyle choices (e.g., smoking) on the use of BIJUVA has not been established.

Interaction with alcohol
Acute alcohol ingestion during use of HRT may lead to elevations of circulating estradiol levels.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 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-17β (E2) is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

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. The production of estradiol by the ovaries is under the control of pituitary gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). Circulating estrogens modulate LH and FSH, through a negative feedback mechanism. In menopausal women, the depletion of ovarian follicles leads to lower plasma estradiol and elevated plasma FSH and LH.

The addition of progesterone opposes the development of endometrial hyperplasia thought to be caused by estrogens.

10.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with BIJUVA.

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

Loss of ovarian estradiol-17β production after menopause can result in instability of thermoregulation, causing hot flushes associated with sleep disturbance and excessive sweating. Estrogen replacement therapy has been used to reduce the number and intensity of hot flushes associated with menopause.

Clinical Pharmacology of Progestins
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.

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The addition of a progestin, in adequate doses and appropriate duration, to an estrogen replacement regimen reduces the incidence of endometrial hyperplasia, and the attendant risk of carcinoma in women with an intact uterus.

10.3 Pharmacokinetics

Absorption: The oral absorption of both estradiol and progesterone is subject to first pass metabolism. After multiple doses of BIJUVA 1 mg estradiol/100 mg progesterone or 0.5 mg Estradiol/100 mg Progesterone, the t_{max} (the time at which the maximum concentration is attained) for estradiol is approximately 5 hours and approximately 3 hours for progesterone (Table 3, below). Steady state for both estradiol and progesterone components of BIJUVA, as well as estradiol's main metabolite, estrone, is achieved within 7 days.

Table 3. Mean (SD) Steady-State Pharmacokinetic Parameters after Administration of Capsules Containing 1 mg Estradiol/100 mg Progesterone or 0.5 mg Estradiol/100 mg Progesterone in Healthy Postmenopausal Women (Baseline Adjusted, at Day 7)

Dosage Strength (estradiol/progesterone)	BIJUVA 1 mg/100 mg Mean (SD)		BIJUVA 0.5 mg/100 mg Mean (SD)	
Estradiol	**N**		**N**	
AUC_{τ} (pg·h/mL)	20	772.4 (384.1)	17	386.8 (356.6)
C_{max} (pg/mL)	20	42.27 (18.60)	17	23.95 (16.86)
C_{avg} (pg/mL)	19	33.99 (14.53)	17	16.64 (14.50)
t_{max} (h)	19	4.93(4.97)	17	5.90 (4.44)
$t_{½}$ (h)*	19	26.47 (14.61)	11	28.01 (9.99)[a]
Estrone	**N**		**N**	
AUC_{τ} (pg·h/mL)	20	4594 (2138)	17	1981 (976.0)
C_{max} (pg/mL)	20	238.5 (100.4)	17	108.0 (48.58)
C_{avg} (pg/mL)	20	192.1 (89.43)	17	82.81 (40.80)
t_{max} (h)	20	5.45 (3.47)	17	8.48 (4.87)
$t_{½}$ (h)*	19	22.37 (7.64)	17	20.46 (5.61)
Progesterone	**N**		**N**	
AUC_{τ} (ng·h/mL)	20	18.05 (15.58)	17	12.19 (11.01)
C_{max} (ng/mL)	20	11.31 (23.10)	17	4.40 (5.72)
C_{avg} (ng/mL)	20	0.76 (0.65)	17	0.55 (0.45)
t_{max} (h)	20	2.64 (1.51)	17	2.89 (2.29)
$t_{½}$ (h)	18	9.98 (2.57)	13	8.77 (2.78)

*Effective $t_{½}$. Calculated as 24•ln(2)/ ln(accumulation ratio/(accumulation ratio-1)) for subjects with accumulation ratio >1.

[a] Results exclude Subjects 01-833 and 01-836 with accumulation ratios of 371.7 and 43.86, respectively, and effective $t_{½}$ of 6174 hours and 721.3 hours, respectively. With Subjects 01-833and 01-836 included, the mean accumulation ratio is 26.04 and the mean effective $t_{½}$ is 554.1 hours.

$AUC_{0-\tau}$ = 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.

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. Estradiol circulates in the blood bound to SHBG (37%) and to albumin (61%), while only approximately 1% to 2% is unbound.

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

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.

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 (Table 3).

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.

Special Populations and Conditions

Pediatrics: No pharmacokinetic study for BIJUVA has been conducted in a pediatric population. BIJUVA is not indicated in the pediatric population.

Geriatrics: BIJUVA has not been studied in women over 65 years old; therefore, BIJUVA is not recommended in women over 65 years of age.

Sex: BIJUVA is indicated for use in postmenopausal women only.

Pregnancy and Breast-feeding: BIJUVA is contraindicated in women who are pregnant or breast-feeding (see **CONTRAINDICATIONS**).

Ethnic origin: No studies were done to determine the effect of race on the pharmacokinetics of

BIJUVA.

Hepatic Insufficiency: BIJUVA is contraindicated in women with liver dysfunction or disease as long as liver function tests have failed to return to normal (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Renal Insufficiency: BIJUVA is to be used with caution in women with renal dysfunction (see **WARNINGS AND PRECAUTIONS**).

Obesity: No studies were done to determine the effect of body weight on the pharmacokinetics of BIJUVA.

11 STORAGE, STABILITY AND DISPOSAL

Store BIJUVA at room temperature (15 to 25°C). Protect from light. Keep out of sight and reach of children.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Estradiol

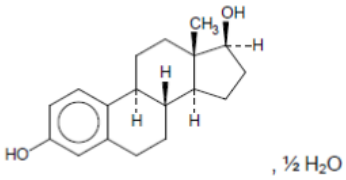
Proper name: Estradiol hemihydrate

Chemical name: Estra-1,3,5(10)-triene-3, 17β-diol, hemihydrate

Molecular formula: $C_{18}H_{24}O_2$, 1/2 H_2O

Molecular mass: 281.39

Structural formula:



Physicochemical properties: White or almost white, crystalline powder, or colorless crystals; practically insoluble in water, soluble in acetone and in ethyl alcohol (96%); slightly soluble in ether and methylene chloride. Melting range between 173°C and 179°C.

Drug Substance

Progesterone

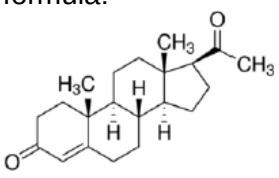
Proper name: Progesterone

Chemical name: Pregn-4-ene-3,20-dione

Molecular formula: $C_{21}H_{30}O_2$

Molecular mass: 314.47

Structural formula:



Physicochemical properties: White or almost white, crystalline powder, or colorless crystals; practically insoluble in water, freely soluble in ethanol, sparingly soluble in acetone and fatty oils. Melting range between 126°C and 131°C.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

The efficacy and safety of BIJUVA (estradiol and progesterone) capsules on moderate to severe vasomotor symptoms (hot flushes) due to menopause were examined in a 12-week randomized, double-blind, placebo-controlled sub-study of a single 52-week safety study. A total of 726 postmenopausal women were randomized to multiple dose combinations of estradiol (E2) and progesterone (P), 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.

In the sub-study evaluating effects on moderate to severe vasomotor symptoms, 141 subjects received BIJUVA 1 mg estradiol/100 mg progesterone, 149 subjects received BIJUVA 0.5 mg estradiol/100 mg progesterone and 135 subjects received placebo and comprised the primary efficacy population. The mean number of years since last menstrual period was 5.9 years, with 718 (98.9%) women undergoing natural menopause while 8 (1.1%) women reported prior bilateral oophorectomy. The primary efficacy population consisted of women who self-identified their race as: White (67%), Black/African American (31%), and “Other” (2.1%).

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. Menopause Specific Quality of Life (MENQOL)[8] was evaluated as a secondary endpoint.

13.2 Study Results

Overall, BIJUVA 1 mg estradiol/100 mg progesterone and 0.5 mg estradiol/100 mg progesterone statistically significant 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 4 and Table 5, respectively. The mean reduction in frequency and severity of weekly moderate and severe vasomotor symptoms from Week 1 through Week 12 for the MITT-VMS population are shown in Figure 1 and Figure 2, respectively.

Mean decreases from baseline in the MENQOL scores (vasomotor domain and total score) were significantly greater in the BIJUVA 1 mg estradiol/100 mg progesterone and 0.5 mg estradiol/100

[8] The MENQOL questionnaire is self-administered and assesses changes in quality of life over a one month period. It is composed of 29 questions distributed across four domains: vasomotor, psychosocial, physical, and sexual. Each domain score ranged from 1 to 8. The MENQOL was administered at Randomization, Week 12, Month 6, and Month 12 or Early Termination.

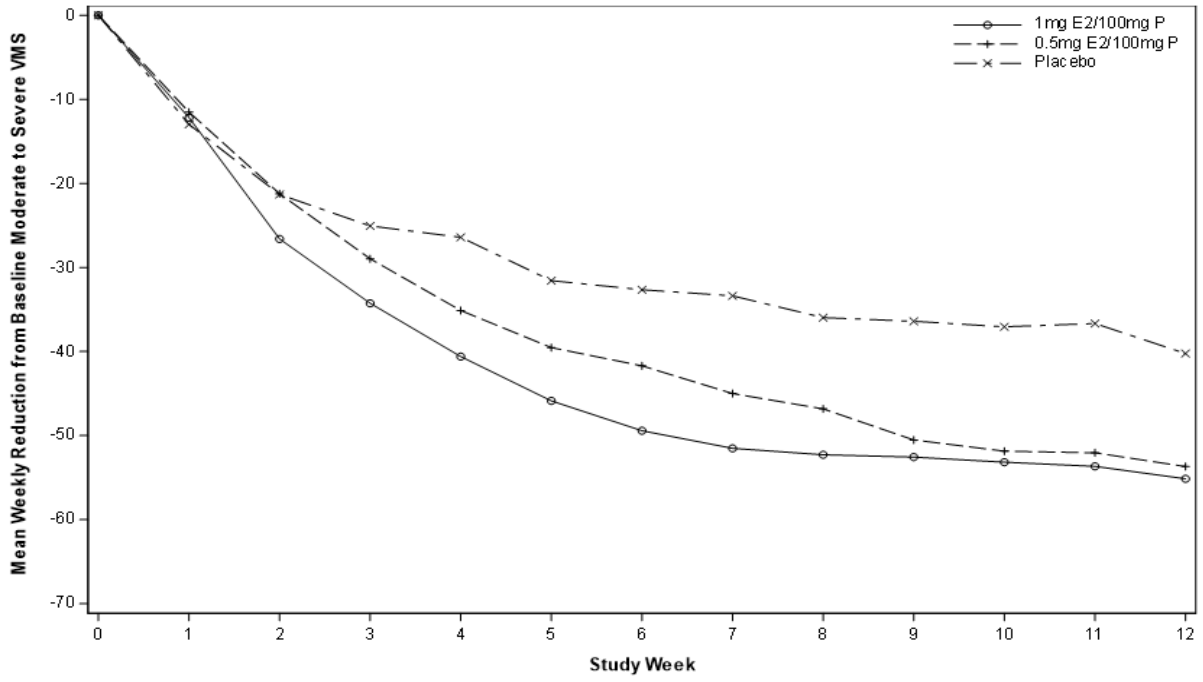
mg progesterone treatment groups compared to placebo at Week 12, Month 6, and Month 12 ($p<0.05$).

Table 4. Mean Weekly Change from Baseline and LS Mean Change from Placebo in the Frequency of Moderate to Severe Vasomotor Symptoms

	BIJUVA 1 mg E2/100 mg P (N=141)	**BIJUVA 0.5 mg E2/100 mg P (N=149)**	**Placebo (N=135)**
Week 4	n=134	n=144	n=126
Baseline	72.1 (27.80)	72.3 (28.06)	72.3 (23.44)
Mean (SD) change from baseline	-40.6 (30.59)	-35.1 (29.14)	-26.4 (27.05)
LS Mean (SE) change from placebo	-12.81 (3.30)	-8.07 (3.25)	---
MMRM p-value	< 0.001	0.013	---
Week 12	n=124	n=129	n=115
Baseline	72.2 (25.04)	72.8 (28.96)	72.2 (22.66)
Mean (SD) change from baseline	-55.1 (31.36)	-53.7 (31.93)	-40.2 (29.79)
LS Mean (SE) change from placebo	-16.58 (3.44)	-15.07 (3.39)	---
MMRM p-value	<0.001	<0.001	---

Definitions: SD – standard deviation; SE – standard error; LS – least square; MMRM – mixed model repeated measures

Figure 1. Mean Reduction in Frequency of Weekly Moderate to Severe Vasomotor Symptoms from Week 1 Through Week 12 (MITT-VMS Population)



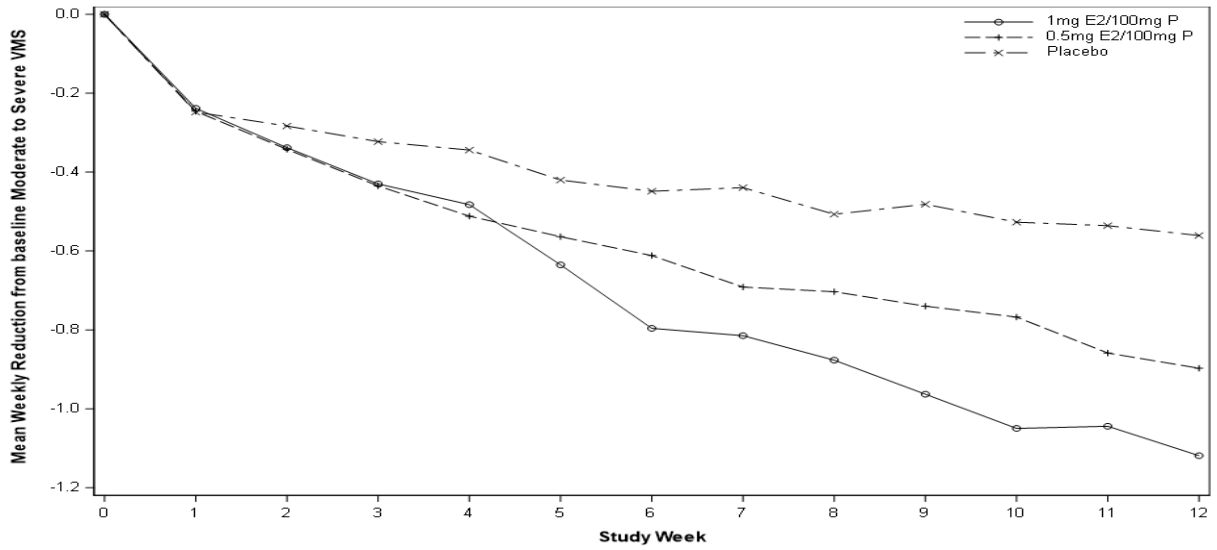
Definitions: MITT-VMS – modified intent to treat – vasomotor symptoms; E2 – 17β-estradiol; P – progesterone

Table 5. Mean Weekly Change from Baseline and LS Mean Change from Placebo in the Severity of Moderate to Severe Vasomotor Symptoms

	BIJUVA 1 mg E2/100 mg P (N=141)	**BIJUVA 0.5 mg E2/100 mg P (N=149)**	**Placebo (N=135)**
Week 4	n=134	n=144	n=126
Baseline	2.54 (0.325)	2.51 (0.248)	2.52 (0.249)
Mean (SD) change from baseline	-0.48 (0.547)	-0.51 (0.563)	-0.34 (0.386)
LS Mean (SE) change from placebo	-0.13 (0.061)	-0.17 (0.060)	---
MMRM p-value	0.031	0.005	---
Week 12	n=124	n=129	n=115
Baseline	2.55 (0.235)	2.51 (0.248)	2.52 (0.245)
Mean (SD) change from baseline	-1.12 (0.963)	-0.90 (0.783)	-0.56 (0.603)
LS Mean (SE) change from placebo	-0.57 (0.100)	-0.39 (0.099)	---
MMRM p-value	<0.001	<0.001	---

Definitions: SD – standard deviation; SE – standard error; LS – least square; MMRM – mixed model repeated measures

Figure 2. Mean Reduction in Severity of Weekly Moderate to Severe Vasomotor Symptoms from Week 1 Through Week 12 (MITT-VMS Population)



Definitions: MITT-VMS – modified intent to treat – vasomotor symptoms; E2 – 17β-estradiol; P – progesterone

In a subgroup analysis, treatment with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg and 0.5 mg/100 mg, did not demonstrate statistically significant reductions in frequency and

severity of moderate to severe vasomotor symptoms compared to placebo in women who self-identified as Black/African Americans. The effectiveness of BIJUVA in Black/African Americans to reduce moderate to severe vasomotor symptoms has not been established.

Effects on Endometrium
Effects of BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg and 0.5/100 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 capsules and had baseline and post-baseline endometrial biopsies. During the trial, endometrial biopsy assessments revealed 1 case of endometrial hyperplasia in women who received BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, and 1 case of endometrial hyperplasia in women who received 0.5 mg/100 mg (see Table 6). No cases of hyperplasia were observed in women who received placebo. No cases of endometrial cancer were observed in the 52-week safety trial.

Table 6. Incidence of Endometrial Hyperplasia After up to 12 Months of Treatment

	BIJUVA 1 mg E2/100 mg P (N=281)	**BIJUVA 0.5 mg E2/100 mg P (N=303)**	**Placebo (N=92)**
Hyperplasia incidence rate % (n/N)	0.36% (1/281)	0.33% (1/303)	0.00% (0/92)
One-sided upper 95% confidence limit	1.97%	1.83%	3.93%

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 1 mg estradiol/100 mg progesterone; 67.6% who received 0.5 mg estradiol/100 mg progesterone and 78.9% who received placebo.

14 NON-CLINICAL TOXICOLOGY

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

Carcinogenicity
Carcinogenicity of 17β-estradiol and progesterone are well-established in the literature.

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.

For 17β-estradiol, long-term studies in mice demonstrate that oral administration of 0.00188, 0.015, 0.15 and 0.75 mg/kg/day in mice can increased the incidences of mammary, uterine, cervical and ovarian tubular tumours. In rats administered 10-12 mg/animal by subcutaneous pellet, there was an increased incidence of mammary and pituitary tumours.

Subcutaneous implantation of progesterone pellets in mice resulted in increases in ovarian

granulosa cell tumors and endometrial sarcomas, metaplasia in the endocervical mucosa, squamous cell carcinomas of the cervicovaginal region and hyperplastic nodules of the mammary gland. The findings of tumors in the reproductive tissues of rodents are consistent with that observed with other progestational compounds.

Genotoxicity
Genotoxicity of 17β-estradiol and progesterone are well-established in the literature.

The clastogenic potential of 17 β-estradiol was evident from the chromosome aberrations and sister chromatid exchanges induced with and without metabolic activation in cultured human lymphocytes and from the increased frequencies of micronuclei formation and sister chromatid exchanges in mice. However, 17 β-estradiol is not considered to be mutagenic as a negative response was observed in the *in vitro* Ames bacterial reverse mutation assay.

Progesterone was negative *in vitro* for point mutations in the Ames test, in *E. coli* bacteria, and in the mouse lymphoma forward mutation assay.

Progesterone did not cause mitotic disturbances or chromosome aberrations in Chinese hamster fibroblast cells in culture and did not cause an increase in unscheduled DNA synthesis in hepatocytes from male Fischer 344 rats in culture.

Progesterone was negative in assays for chromosome damage using human female leukocytes, or by the sister chromatid exchange (SCE) assay in human female peripheral blood lymphocytes (HPBL) or in human fibroblast cells.

Chromosome changes were observed in Chinese hamsters receiving SC injections of progesterone for up to four weeks, and in the testes of male mongrel dogs injected IM every other day for six weeks. Since the doses in these studies would have produced blood levels of progesterone in the endogenous range, the toxicological significance of the results is unclear.

Reproductive and Developmental Toxicology
Reproductive toxicity of 17β-estradiol and progesterone are well-established in the literature.

17 β-estradiol administered in the feed to female Crl:CD BR rats at doses equal to 0, 0.003, 0.173, 0.691, or 4.12 mg/kg/day and to males at doses equal to 0, 0.003, 0.139, 0.527, or 3.16 mg/kg/day resulted in a decreased in the number of matings and no pregnancies at the two highest doses. For the three groups with pregnancies (0, 0.003, 0.173 mg/kg/day), there was no difference in gestation length, however, gestation body weight gain, food consumption, and mean number of implants were affected. Mean number of live births was significantly decreased in the 0.173 mg/kg/day group compared to control.

Parental administration of 17 β-estradiol did not affect the anogenital distance in male or female pups. For the onset of sexual maturity, preputial separation in male pups in the 0.17 mg/kg/day group was significantly delayed. In female pups, a decrease in time (advancement) for the vaginal opening was noted in both the 0.003 and 0.173 mg/kg/day dosed groups. The F1 generation was not mated.

In white rabbits, intramuscular estradiol administration at 15 or 30 µg/animal for 3-6 consecutive days at different times during gestation resulted in 67 and 78% aborted or totally resorbed litters and 4% and 17% of litters with dead fetuses, respectively.

Administration of progesterone by SC injection to pregnant mice resulted in a decrease in sexual behavior in male offspring with no changes to internal or external genitalia, and an increase in aggressive behavior in female offspring. No abnormalities of internal or external genitalia were observed in the offspring of rats treated with progesterone by SC injection.

No adverse effect on egg development was observed following oral (gavage) administration of progesterone to rabbits three days before or after mating. SC dosing of pregnant rabbits also had no adverse effect on egg development, while SC dosing two days prior to mating induced complete degeneration of eggs. Single SC injection to rabbits before mating did not impair fertility but led to embryonic death by day 4 of gestation.

Administration of progesterone by IM injection to pregnant rhesus monkeys did not cause any adverse effects on pregnancy or on the incidence of anomalies in the offspring.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrBIJUVA™
0.5 mg estradiol/100 mg progesterone
1 mg estradiol/100 mg progesterone

Read this carefully before you start taking **BIJUVA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BIJUVA.**

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial was a large clinical study. This study assessed the benefits and risks of two oral therapies (combined estrogen plus progestin and estrogen-alone) compared with placebo (a pill with no active ingredients) in postmenopausal women.

In postmenopausal women taking oral combined estrogen plus progestin, the WHI trial indicated an increased risk of:

- myocardial infarction (heart attack),
- stroke,
- breast cancer,
- pulmonary emboli (blood clots in the lungs), and deep vein thrombosis (blood clots in the large veins).

In postmenopausal women taking oral estrogen-alone, who had a prior surgery to remove the uterus (called a hysterectomy), the WHI trial indicated an increased risk of:

- stroke, and
- deep vein thrombosis.

Therefore, the following should be considered and discussed with your healthcare professional:

- Estrogens with or without progestins **should not** be used for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be used at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be used for **the shortest period** possible for the approved indication.

What is BIJUVA used for?
BIJUVA is used to reduce and relieve vasomotor symptoms (hot flashes and night sweats). It is only used in postmenopausal women with an intact uterus.

How does BIJUVA work?
BIJUVA provides 2 types of sex hormones, called estradiol and progesterone, to the body.

Estradiol is a type of estrogen. Progesterone is a type of progestogen. Estrogen acts on different tissues in the body to help treat symptoms of menopause.

Like estrogens produced by your body, BIJUVA may also cause overgrowth of the lining of the uterus. This may increase the risk of endometrial cancer (cancer of the lining of the uterus). The risk is lowered if progesterone is given together with estrogen.

What are the ingredients in BIJUVA?
Medicinal ingredients: estradiol (as estradiol hemihydrate) and progesterone.
Non-medicinal ingredients: FD&C Red #40, gelatin, glycerin, hydrolyzed gelatin, lauryl polyoxyl-32 glycerides, lecithin, medium chain mono and di-glycerides, medium chain triglycerides, pharmaceutical ink, purified water, and titanium dioxide.

BIJUVA comes in the following dosage forms:
Oral capsules provided in two strengths:
- 1 mg estradiol / 100 mg progesterone;
- 0.5 mg estradiol / 100 mg progesterone.

Supplied in blister package of 30 capsules or samples of 5 capsules.

Do not use BIJUVA if you:
- Are allergic to any ingredients in this drug or the container;
- Have or have had liver disease, and blood tests to measure how your liver is working have not returned to normal;
- Have, might have or had cancer that is sensitive to estrogens or progestin (e.g. breast cancer or endometrial cancer);
- Have an untreated overgrowth of the lining of the uterus (endometrial hyperplasia);
- Have (or have had) a personal history of known or suspected breast cancer;
- Have unexplained bleeding from the vagina;
- Are pregnant or maybe pregnant;
- Are breast-feeding;
- Have or have had a heart attack, stroke, a blockage or narrowing of the arteries around the heart (called coronary heart disease);
- Have migraine (headaches);
- Have or have had blood clotting problems:
  - deep vein thrombosis (blood clots in big veins);
  - pulmonary embolism (blood clots in the lung);
  - thrombophlebitis (inflammation of a vein caused by a blood clot);
- Have eye problems that are caused by low blood flow to the eyes.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BIJUVA. Talk about any health conditions or problems you may have, including if you:
- Have or had uterus problems:
  - Fibroids (growths) inside your uterus;
  - Endometriosis (growth of the uterine lining outside your uterus);
  - A history of endometrial hyperplasia (overgrowth of the lining of the uterus);
  - have had a hysterectomy (surgical removal of the uterus).
- Have a personal or family history of:
  - breast problems (including breast lumps and breast cancer);
  - blood clots, heart disease or stroke.

- Have a history of allergy or intolerance to any drugs or other substances;
- Have or had any vaginal bleeding that is not normal;
- Have ear problems affecting the eardrum and hearing called otosclerosis;
- Have a history of liver problems like liver tumours (hepatic hemangioma), yellowing of the eyes and/or skin (jaundice) or itching;
- Been told that you have a condition called hereditary angioedema or if you have had events of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage), or digestive tract;
- Have or had migraine, headaches, trouble speaking, paralysis or loss of consciousness. These are symptoms of blood blockage to the brain.
- Have or had high blood pressure;
- Have or had asthma;
- Have kidney problems;
- Have seizures (epilepsy);
- Have disease of the immune system that affects many organs of the body. This is called systemic lupus erythematosus.
- Have or had bone disease (this includes certain conditions or cancers that can affect blood levels of calcium and phosphorus);
- Have low or high levels of calcium;
- Have or had diabetes or a family history of diabetes;
- Have or had high levels of fat in your blood (cholesterol, triglycerides);
- Are pregnant, may be pregnant or breastfeeding;
- Had or will have surgery;
- Have a disease that affects how the blood functions (porphyria);
- Have thyroid problems;
- Have biliary problems (gallbladder disease, bile problems);
- Smoke.

BIJUVA is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Speak to your doctor for advice.

Other warnings you should know about:
Breast Cancer
There is a risk for breast cancer in women taking HRT for many years.

Regarding breast cancer, the WHI trial showed:
- An increased risk of breast cancer in postmenopausal women taking combined estrogen plus progestin.
- No difference in the risk of breast cancer in postmenopausal women with a previous hysterectomy taking estrogen-alone.

If you have had breast cancer, you should not take estrogens with or without progestins.

If you have a family history of breast cancer or have had breast lumps, breast biopsies or abnormal mammograms (breast x-rays), talk to your healthcare professional before starting HRT.

Check your breasts often. See your healthcare professional if you notice any changes, such as:

- Dimpling or sinking of the skin;
- Changes in the nipple; or
- Any lumps you can see or feel.

Ovarian Cancer
Women who take estrogen-only or combined HRT (estrogen-progestin) for 5 or more years have a slightly higher chance of ovarian cancer.

Overgrowth of the lining of the uterus and cancer of the uterus
There are reports of endometrial hyperplasia (overgrowth of the lining of the uterus) seen in women using BIJUVA.

The use of estrogen-alone increases the risk of developing endometrial hyperplasia, which increases the risk of endometrial cancer (cancer of the lining of the uterus). These risks apply to post-menopausal women with a uterus.

Progestin is added to estrogen therapy to reduce the risk of endometrial hyperplasia.

Talk to your healthcare professional about the risk factors for overgrowth and cancer of the uterus lining. You should report any unexpected or unusual vaginal bleeding.

Heart Disease (Heart Attack) and Stroke
The WHI trial showed:
- An increased risk of stroke and coronary heart disease in postmenopausal women taking combined estrogen plus progestin.
- An increased risk of stroke, but no difference in the risk of coronary heart disease in postmenopausal women with a previous hysterectomy taking estrogen-alone.

Abnormal Blood Clotting (including pulmonary embolism and deep vein thrombosis)
The WHI trial showed:
- An increased risk of pulmonary emboli and deep vein thrombosis (blood clots in the lung and in big veins) in postmenopausal women taking combined estrogen plus progestin.
- An increased risk of deep vein thrombosis, but no difference in the risk of pulmonary emboli in postmenopausal women with previous hysterectomy taking estrogen-alone.

You are more likely to get a blood clot in your veins as you get older. Blood clots can be life-threatening or cause serious disability. Talk to your healthcare professional if any of the below situations apply to you:
- You use estrogens;
- You are unable to walk for a long time because of a major surgery, injury or sickness;
- You are overweight and your BMI is greater than 30;
- You have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots;
- Any of your close relatives has ever had a blood clot in the leg, lung or another organ;
- You smoke;
- You have systemic lupus erythematosus (an autoimmune disease);
- You have cancer.

If you are going to have a surgery, tell your healthcare professional that you are taking BIJUVA. You may need to stop taking BIJUVA at least 4 weeks before the surgery to reduce the risk of

a blood clot. Ask your healthcare professional when you can start taking BIJUVA again.

Gallbladder Disease
The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease that needs surgery.

Dementia
The Women's Health Initiative Memory Study (WHIMS) was a sub-study of the WHI trial. The WHIMS study showed:
- An increased risk of dementia (loss of memory and intellectual function) in postmenopausal women age 65 and over who were taking oral combined estrogen plus progestin.
- No difference in the risk of dementia in postmenopausal women aged 65 and over who had previously had a hysterectomy and were taking oral estrogen-alone.

Physical exam, tests, and check-ups:
Before you start taking BIJUVA, you will need to have examinations and tests. These will include a physical exam, a Pap smear and a breast exam. Your healthcare professional will ask you about your personal and your family's health history. You will also have your blood pressure taken as well as blood tests and a mammogram (breast x-ray). A uterus tissue sample might be needed.

While you are taking BIJUVA, check your breasts often and get regular check-ups with your healthcare professional.

Your first check-up should be within 3 to 6 months of starting BIJUVA. Thereafter, these should be scheduled at least once a year. These check-ups will help to identify any side effects you may have. Your visits may include a blood pressure check, a breast exam, a Pap smear, and pelvic exam. You will also have repeat mammograms and blood tests. Your healthcare professional will decide when these are necessary and will interpret the results.

Geriatrics (> 65 years of age):
- BIJUVA is not recommended for use in women over 65 years of age.

Children less than 18 years of age:
- BIJUVA is not for use in children less than 18 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BIJUVA:
- Drugs used for the prevention or treatment of blood clots (anticoagulants), such as warfarin;
- Drugs used to treat diabetes, such as glyburide and insulin;
- Drugs used to treat viral infections, such as ritonavir, nelfinavir, amprenavir and fosamprenavir;
- Drugs used to treat high blood pressure, such as verapamil and diltiazem;
- Drugs that impact liver enzymes, such as barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin;
- Drugs used to treat epilepsy and seizures (anticonvulsants), such as phenobarbital, phenytoin, oxcarbazepine and topiramate;
- St. John's Wort, used to treat depression;

- Drugs used to treat bacterial or viral infections, such as clarithromycin, erythromycin, rifampin, and rifabutin;
- Drugs used to treat fungal infections, such as ketoconazole, fluconazole and itraconazole;
- Drugs used for the treatment of HIV infections and Hepatitis C Virus infections, such as nelfinavir, ritonavir, boceprevir, telaprevir, efavirenz and nevirapine;
- Grapefruit juice;
- Alcohol.

How to take BIJUVA:
- Always take BIJUVA exactly as your healthcare professional has told you.
- Take BIJUVA, by mouth, each evening with food.

Usual Adult Dose:
- One capsule per day.

Your healthcare professional will monitor your health. They may interrupt, change, or stop your dose. This may occur based on your current health, if you take certain other medications or if you have certain side effects.

Overdose:
Signs of an overdose may include feeling sick, breast discomfort, fluid retention, bloating and vaginal bleeding. Other signs may include feeling sad, tiredness, acne, and excess hair growth.

If you think you have taken too much BIJUVA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take a capsule, take it as soon as you remember. However, if the dose is close to the next scheduled dose, skip the missed dose and continue with your next scheduled dose. Do not take a double dose to make up for a missed one. If you forget several capsules, you may get some slight vaginal bleeding or spotting.

What are possible side effects from using BIJUVA?
These are not all the possible side effects you may feel when taking BIJUVA. If you experience any side effects not listed here, contact your healthcare professional.

- Headache, dizziness, irritability
- Stomach, abdominal, back and joint pain
- Pelvic pain and cramping
- Nausea
- Diarrhea
- Feeling bloated and gassy
- Feeling tired (fatigue)
- Weight gain
- Vaginal bleeding, spotting, discharge
- Vaginal infection: discomfort, pain, odor, itching
- Urinary tract infection: pain or burning feeling when urinating
- Loss of scalp hair

- Excess hair on face, chest, abdomen or legs
- Breast tenderness, pain, swelling
- Acne, rash, dry and itchy skin

BIJUVA can cause abnormal blood test results. Your healthcare professional will decide when these are necessary and will interpret the results. They will tell you if your test results are abnormal and if you need treatment.

The risks related to oral estrogen should be considered as well. Serious side effects that are possible with BIJUVA, as well as oral estrogen, are listed in the table below.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Breast abnormalities (including breast cancer): dimpling or sinking of the skin, changes in the nipple, or any lumps you can see or feel, discharge from breasts, enlarged breasts, swelling		√	
Gallbladder problems: fever, nausea, pain that radiates to your shoulder or back, severe pain in your upper right abdomen, vomiting	√		
Deep vein thrombosis (blood clot in the legs) or **Thrombophlebitis** (inflammation of a vein often in the leg): sudden leg swelling or pain; redness, warmth, tenderness and pain in affected area			√
Hypersensitivity (allergic reaction): fever, skin rash, hives, itching, swelling, shortness of breath, wheezing, runny nose, itchy, watery eyes			√
Dementia (memory and thinking problems): memory loss, impaired thinking, difficulty speaking, loss of control of body movements, disorientation, trembling		√	
Stroke (blood clot in the brain): sudden severe headache, vomiting, dizziness, fainting, problems with your vision or speech, weakness or numbness in the face, arm, or leg			√
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid pulse, nausea, vomiting, tenderness when touching the abdomen		√	
Pulmonary embolism (blood clot in the lungs): sharp chest pain, coughing up blood, or sudden shortness of breath			√
RARE			
Coronary artery disease (blocked or narrowing of heart arteries): crushing chest pain and pressure, shortness of breath			√

Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness or hopelessness, withdrawal from social situations, reduced libido (sex drive) and thoughts of death or suicide.			√
Endometrial hyperplasia or cancer (abnormal growth or cancer of the lining of the uterus): unexpected, abnormal and/or severe vaginal bleeding		√	
Erythema multiforme (an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning			√
Erythema nodosum (swelling of the fat cells under the skin): Tender red lumps usually on both shins	√		
Neuro-ocular lesions (damaged eye nerves): blurred vision, sudden complete or partial loss of vision in eye, eye pain			√
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, blush colour to your lips and skin, racing pulse or heart palpitations		√	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, light coloured stool, unusual tiredness			√
Ovarian cancer: abdominal pain or bloating, quickly feeling full after eating, weight loss, pain in pelvis, change in bowel habits, need to urinate often		√	
Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands, feeling heavy, achy or stiff	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store the container at room temperature (15 - 25°C).
Protect from light.
Keep out of sight and reach of children.

If you want more information about BIJUVA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (https://www.gud-knight.com/), by emailing medinfo@gudknight.com, or by calling 1-844-483-5636.

This leaflet was prepared by Knight Therapeutics Inc.

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