ON AVERAGE, WOMEN SPEND UP TO 1/3 OF THEIR LIVES IN MENOPAUSE[1,2]

PRODUCTS DESIGNED TO HELP WOMEN
THROUGHOUT THEIR MENOPAUSE JOURNEY

Imvexxy®
(estradiol vaginal inserts)
4 mcg • 10 mcg

FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

Bijuva® 1mg/100mg
(estradiol and progesterone) capsules

FOR THE TREATMENT OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS (HOT FLASHES) DUE TO MENOPAUSE IN WOMEN WITH A UTERUS

IMVEXXY AND BIJUVA IMPORTANT SAFETY INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, PROBABLE DEMENTIA and BREAST CANCER
See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT)**
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older**
- **Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia**

Estrogen Plus Progestin Therapy

- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE) and myocardial infarction (MI)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older**
- **Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia**

The WHI estrogen-alone and estrogen plus progestin substudies evaluated only daily oral conjugated estrogens (CE) [0.625 mg] and medroxyprogesterone acetate (MPA) [2.5 mg]. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia, and breast cancer to lower CE and MPA doses, other routes of administration, or other estrogen-alone or estrogen plus progestogen products is not known, and cannot be definitively excluded or determined.

IMVEXXY AND BIJUVA have not been studied to be used together.

Please see Important Safety Information, including BOXED WARNING, throughout and the accompanying Full Prescribing Information.

IMVEXXY PROVIDES FAST RELIEF
FOR MODERATE TO SEVERE DYSPAREUNIA[3-5]

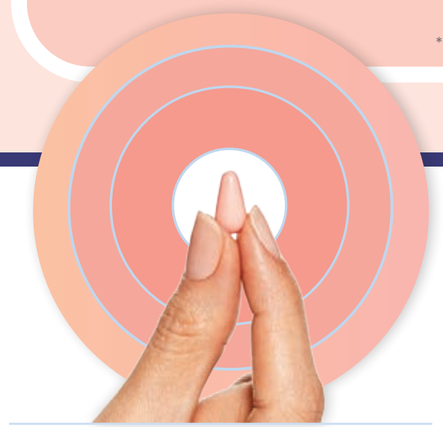
Relief as early as 2 weeks[3-5]*

Ultra-low dose[5,6]

Mess-free administration[3,5,7]

Convenient dosing on her schedule[5,7]

*Secondary endpoint from a 12-week clinical trial.[4]



Imvexxy®
(estradiol vaginal inserts)
4 mcg • 10 mcg

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

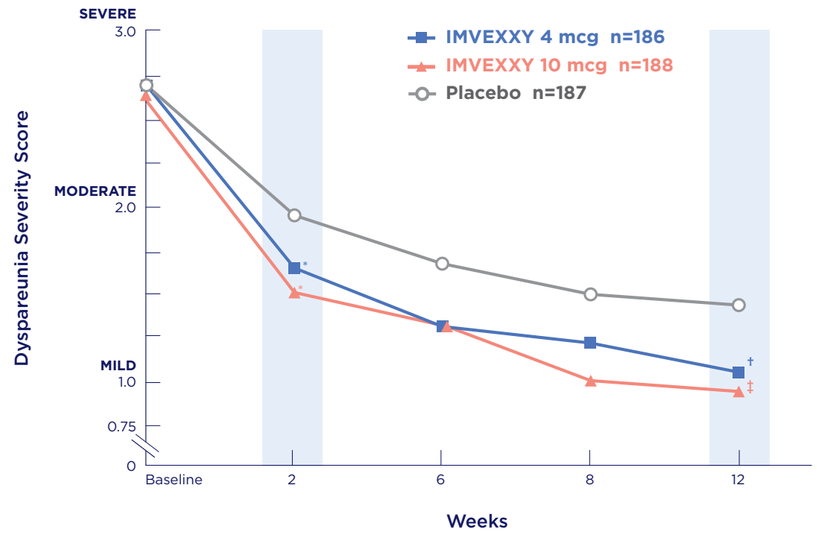
- IMVEXXY (estradiol vaginal inserts) is contraindicated in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease or a history of these conditions; known anaphylactic reaction or angioedema to IMVEXXY; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

Please see additional Important Safety Information, including BOXED WARNING, throughout and the accompanying Full Prescribing Information.

IMVEXXY PROVIDES FAST RELIEF
INSIDE AND OUTSIDE THE VAGINA[3-5,8]

AS EARLY AS 2 WEEKS, IMVEXXY helps restore the estrogen lost after menopause to relieve painful symptoms of dyspareunia **inside and outside the vagina.[3-5,8]***

REDUCTIONS IN MODERATE TO SEVERE DYSPAREUNIA DUE TO VVA OVER 12 WEEKS*



*Secondary endpoint included change from baseline to weeks 2, 6, and 8.
†***P*<0.05. ‡*P*<0.0001. *P* value vs placebo based on mixed model repeated measures analysis.**
VVA = vulvar and vaginal atrophy.

WARNINGS AND PRECAUTIONS

- ***Risks from systemic absorption.*** IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY.
- ***Cardiovascular disorders, malignant neoplasms, and probable dementia.*** Please refer to Boxed Warning for endometrial cancer, cardiovascular disorders, probable dementia, and breast cancer.
  - The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

PLACED WHERE IT MATTERS

IMVEXXY is placed comfortably ~2 inches into the lower part of the vagina[5,7]

RAPIDLY DISSOLVING

Softgel insert contains solubilized, bio-identical estradiol that is structurally identical to the estrogen produced in the body[5,7*†]

ABSORBED INSIDE AND OUTSIDE

Estradiol is absorbed into the internal and external vaginal tissue[3,5]

*Solubilized=made to be able to dissolve.
†Bio-identical hormones are structurally identical to the hormones produced within a woman's body. The relevance of risks associated with the use of synthetic hormones compared to bio-identical hormones is not known but cannot be excluded.

"It is preferred to insert vaginal products (except for the vaginal ring) in the proximal, **LOWER THIRD OF THE VAGINA RATHER THAN IN THE UPPER THIRD. THIS IMPROVES EFFICACY** for genitourinary symptoms and attenuates estradiol absorption."[9]

— North American Menopause Society

IMVEXXY STUDY DESIGN[5]

This 12-week, randomized, double-blind, placebo-controlled, parallel-group trial enrolled 574 generally healthy postmenopausal women between 40 and 75 years of age who at baseline had ≤5% superficial cells on a vaginal smear, a vaginal pH >5.0, and self-identified moderate to severe dyspareunia as their most bothersome symptom of vulvar and vaginal atrophy.

Improvement in the mean change from baseline at week 12 was assessed for the co-primary efficacy variables of: most bothersome moderate to severe symptom of dyspareunia, percentage of vaginal superficial and parabasal cells on a vaginal smear, and vaginal pH.

Imvexxy® (estradiol vaginal inserts) 4 mcg • 10 mcg

HOLD
Hold capsule between fingers[5]

INSERT
~2 inches into the vagina[5]

GO
Enjoy everyday activities[7]

~90%
of women said IMVEXXY was easy to use[10*]

*A patient survey evaluated the acceptability of the product administration experience and was completed at the end of the study by women in the 4-mcg, 10-mcg, and matching softgel placebo arms (N=574).[9]

STARTER PACK (MONTH 1)
One insert, once daily for 2 weeks[5]

MAINTENANCE PACK (MONTHS 2+)
One insert, twice weekly[5]

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

- **Other warnings include:** gallbladder disease; severe hypercalcemia, loss of vision, elevated blood pressure, severe hypertriglyceridemia, cholestatic jaundice, fluid retention, and hypocalcemia in women with hypoparathyroidism.

Please see additional Important Safety Information, including BOXED WARNING, throughout and the accompanying Full Prescribing Information.

COMPREHENSIVE **SAFETY PROFILE**

LOW INCIDENCE OF ADVERSE REACTIONS

The most common adverse reaction with IMVEXXY (incidence ≥3% and greater than placebo) was headache.[5]

NO CASES OF ENDOMETRIAL HYPERPLASIA

IMVEXXY demonstrated no cases of endometrial hyperplasia with either dose of IMVEXXY in a 12-week clinical trial.[3]*

*Long-term studies are required to assess the risk associated with continued use. See BOXED WARNING on cover about the risk of endometrial cancer.

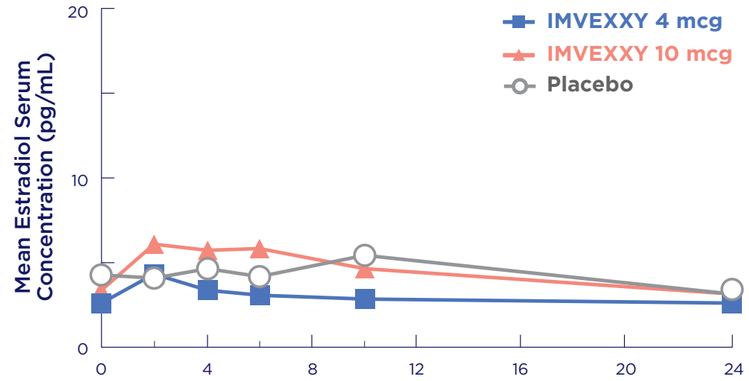
IMPORTANT SAFETY INFORMATION (CONT'D)

- **Estrogen therapy may exacerbate:** hypothyroidism, endometriosis, hereditary angioedema, asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas, and should be used with caution in women with these conditions.
  - Women on thyroid replacement therapy should have their thyroid function monitored.

Please see additional Important Safety Information, including BOXED WARNING, throughout and the accompanying Full Prescribing Information.

4 mcg | 10 mcg

AVERAGE SYSTEMIC ESTRADIOL LEVELS STAYED WITHIN THE NORMAL POSTMENOPAUSAL RANGE FOR BOTH DOSES OF IMVEXXY (N=54).[5]*



The clinical relevance of systemic absorption rates for all vaginal estrogen therapies is not known. Systemic absorption may occur with IMVEXXY. The risks associated with systemic estrogen therapy should be considered.

*A substudy of the REJOICE trial (N=54) evaluated the pharmacokinetics of IMVEXXY 4-mcg and 10-mcg doses once daily for 2 weeks followed by twice weekly for 10 weeks.[5]

ADVERSE REACTIONS

- The most common adverse reaction with IMVEXXY (≥3%) was headache.

INDICATION

IMVEXXY (estradiol vaginal inserts) is an estrogen indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Imvexxy® (estradiol vaginal inserts) 4 mcg • 10 mcg

ONE OF A KIND

THE ONLY FDA-APPROVED BIO-IDENTICAL ORAL COMBINATION HORMONE THERAPY[11-13]*

ONE CAPSULE DAILY

ONE PRESCRIPTION

ONE AFFORDABLE TREATMENT

*Bio-identical hormones are structurally identical to the hormones produced within a woman's body. The relevance of risks associated with the use of synthetic hormones compared to bio-identical hormones is not known but cannot be excluded.

> "Hormone therapy remains the **gold standard** for relief of vasomotor symptoms (VMS)"[9]
>
> —The North American Menopause Society
> 2022 Hormone Therapy Position Statement

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

BIJUVA is contraindicated in women with any of the following conditions: undiagnosed abnormal genital bleeding; breast cancer or a history of breast cancer; estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease (for example, stroke, MI), or a history of these conditions; known anaphylactic reaction, angioedema, or hypersensitivity to BIJUVA; hepatic impairment or disease; protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

Bijuva® 1mg/100mg (estradiol and progesterone) capsules

Please see additional Important Safety Information, including BOXED WARNING, throughout and the accompanying Full Prescribing Information.

EFFECTIVE RELIEF THAT MAKES A MEANINGFUL DIFFERENCE TO HER[11, 14-16]

SIGNIFICANTLY REDUCED HOT FLASHES
AS EARLY AS 4 WEEKS

In a clinical trial, BIJUVA demonstrated statistically significant **improvements in frequency and severity** of moderate to severe vasomotor symptoms vs placebo.[11,12]

IMPROVED QUALITY OF LIFE

As a result of vasomotor symptom relief, women taking BIJUVA demonstrated statistically significant **improvements in the Menopause-Specific Quality of Life (MENQOL)** total score (secondary endpoint).[15]

IMPROVED SLEEP

As a result of vasomotor symptom relief, women taking BIJUVA demonstrated statistically significant **improvement in sleep score** (secondary endpoint) as determined by the Medical Outcomes Study (MOS).[17]

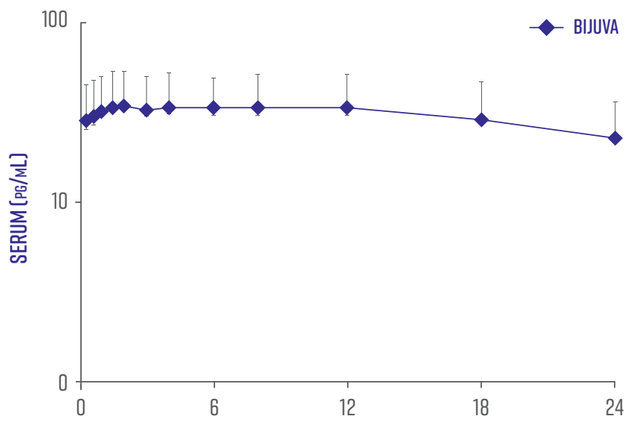
WARNINGS AND PRECAUTIONS

- Increased risks of PE, DVT, stroke, and MI are reported with estrogen plus progestin therapy. Should these occur or be suspected, therapy should be discontinued immediately. Manage appropriately any risk factors for arterial vascular disease and/or venous thromboembolism (VTE).
- The WHI substudy of daily estrogen plus progestin after a mean follow-up of 5.6 years reported an increased risk of invasive breast cancer. Observational studies have also reported an increased risk of breast cancer with estrogen plus progestin therapy after several years of use. The risk increased with duration of use and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

24-HOUR SUSTAINED LEVELS OF ESTRADIOL

BIJUVA demonstrated a steady state of bio-identical estradiol sustained over 24 hours, achieving a steady state at 7 days.[11]

MEAN STEADY-STATE SERUM ESTRADIOL CONCENTRATIONS WITH BIJUVA AT DAY 7[11]



Bijuva® 1mg/100mg
(estradiol and progesterone) capsules

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- Endometrial hyperplasia (a possible precursor to endometrial cancer) has been reported to occur at a rate of approximately 1 percent or less with BIJUVA. Clinical surveillance of all women using estrogen-alone or estrogen plus progestogen therapy is important. Adequate diagnostic measures should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding with unknown etiology.

Please see additional Important Safety Information, including BOXED WARNING, throughout and the accompanying Full Prescribing Information.

BIJUVA STUDY DESIGN[11]

EFFICACY AND SAFETY:

Safety of BIJUVA was assessed in a 1-year, Phase 3 trial that included 1835 postmenopausal women (1684 received multiple dose combinations of estradiol/progesterone capsules once daily. 415 received BIJUVA and 151 received placebo).[12]

The efficacy and safety of BIJUVA were examined in a Phase 3, multicenter, 12-week randomized, double-blind, placebo-controlled substudy of a single 52-week safety study. Participants (N=726) in the study were:

- Randomized to multiple dose combinations of estradiol and progesterone, and placebo;
- 40 to 65 years of age (mean 54.6 years) and having at least 50 moderate to severe vasomotor symptoms (VMS) per week at baseline;
- At a mean of 5.9 years since last menstrual period;
- White (67%), Black/African American (31%), and other (2.1%).

In the efficacy substudy, 141 women received BIJUVA and 135 women received placebo. The evaluated co-primary efficacy endpoints included mean weekly reduction in:

- Frequency and severity of moderate to severe VMS with BIJUVA compared to placebo at weeks 4 and 12.

MENQOL QUESTIONNAIRE:

Menopause-specific quality of life changes in study participants were assessed utilizing the MENQOL (Menopause-Specific Quality of Life) questionnaire, which is self-administered and assesses changes in quality of life over a 1-month period.[15]

MEDICAL OUTCOMES STUDY (MOS) SLEEP SCORE QUESTIONNAIRE:

This questionnaire was utilized to assess changes in sleep for study participants. It was self-administered and provided to subjects at visits 1 (randomization), 4 (week 12), 5 (month 6), and 7 (month 12) or early termination.[17]

- The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.
- In the WHI Memory Study (WHIMS) estrogen plus progestin 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 when compared to placebo. It is unknown whether these findings apply to younger postmenopausal women.

COMPREHENSIVE **SAFETY PROFILE**

IN A 1-YEAR CLINICAL TRIAL

ENDOMETRIAL PROTECTION

Endometrial hyperplasia was reported at a rate of ≤1% in women receiving BIJUVA, consistent with the expected incidence rate in a postmenopausal population.[11,12]

AMENORRHEA RATES

90.2% of women reported no bleeding at cycle 12-13 (~1 year) (secondary endpoint).[12]

ADVERSE EVENTS

Treatment-emergent adverse reactions occurring in ≥3 % of women receiving BIJUVA vs placebo included breast tenderness, headache, vaginal bleeding, vaginal discharge, and pelvic pain.[11]

Bijuva® 1mg/100mg
(estradiol and progesterone) capsules

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- Estrogens increase the risk of gallbladder disease.
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs.
- Monitor thyroid function in women on thyroid replacement hormone therapy.

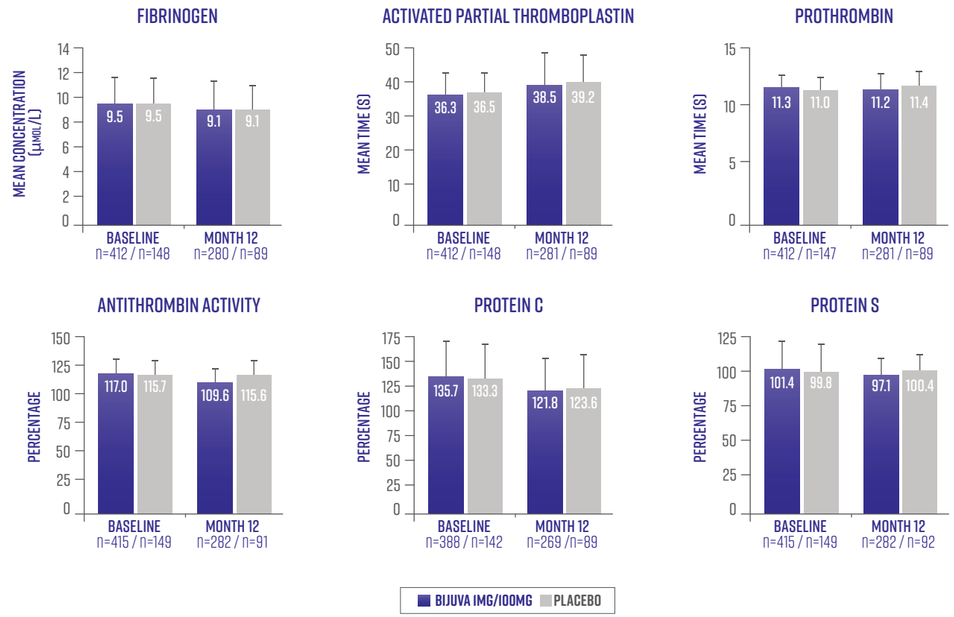
Please see additional Important Safety Information, including BOXED WARNING, throughout and the accompanying Full Prescribing Information.

COAGULATION PARAMETERS

IN A 1-YEAR CLINICAL TRIAL, NO CLINICALLY MEANINGFUL CHANGES IN CARDIOVASCULAR PARAMETERS WERE SEEN FOLLOWING TREATMENT[18]

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI)

COAGULATION FACTORS[18]



IN A 1-YEAR CLINICAL TRIAL, THERE WERE NO STROKES, HEART ATTACKS, OR VENOUS THROMBOEMBOLISMS (PULMONARY EMBOLISM OR DEEP VEIN THROMBOSIS)[18]

- Patients with risk factors for arterial vascular disease and venous thromboembolism, including hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, obesity, personal or family history of (VTE), and systemic lupus erythematosus should be managed appropriately

ADVERSE REACTIONS

The most common adverse reactions (≥3%) with BIJUVA are breast tenderness (10.4%), headache (3.4%), vaginal bleeding (3.4%), vaginal discharge (3.4%) and pelvic pain (3.1%).

NO CLINICALLY MEANINGFUL CHANGES IN:

- CARDIOVASCULAR AND METABOLIC PARAMETERS[12,18]
- WEIGHT[19]
- BLOOD PRESSURE[19]

IN A 1-YEAR CLINICAL TRIAL, THERE WERE NO STROKES, HEART ATTACKS, OR VENOUS THROMBOEMBOLISMS (PULMONARY EMBOLISM OR DEEP VEIN THROMBOSIS)[18]

- Patients with risk factors for arterial vascular disease and venous thromboembolism, including hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, obesity, personal or family history of (VTE), and systemic lupus erythematosus should be managed appropriately

Bijuva® 1mg/100mg
(estradiol and progesterone) capsules

INDICATION

BIJUVA® (estradiol and progesterone) 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.

Please see additional Important Safety Information, including BOXED WARNING, throughout and the accompanying Full Prescribing Information.

REFERENCES

References: 1. Minkin MJ. Menopause: Hormones, lifestyle, and optimizing aging. *Obstet Gynecol Clin North Am.* 2019;46(3):501-514. Abstract. **2.** Clementson G. Pausing to learn more about menopause. Mayo Clinic Health System. November 30, 2021. https://www.mayoclinichealthsystem.org/hometown-health/speaking-of-health/too-embarrassed-to-ask-part-3. Accessed December 15, 2021. **3.** Constantine GD, Simon JA, Pickar JH, et al. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. *Menopause.* 2017;24(4):409-416. **4.** Constantine GD, Millheiser LS, Kaunitz AM, et al. Early onset of action with a 17ß-estradiol, softgel, vaginal insert for treating vulvar and vaginal atrophy and moderate to severe dyspareunia. *Menopause.* 2019;26(11):1259-1264. **5.** Imvexxy [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2021. **6.** Data on file. Vaginal Estrogen Prescribing Information. **7.** Simon JA, Pickar JH, Shadiack AM, et al. Physical characteristics and properties of estradiol softgel vaginal inserts. *Menopause.* 2020;27(2):150-155. **8.** Simon JA, Archer DF, Kagan R, et al. Visual improvements in vaginal mucosa correlate with symptoms of VVA: data from a double-blind, placebo-controlled trial. *Menopause.* 2017;24(9):1003-1010. **9.** North American Menopause Society. The 2022 hormone therapy position statement of The North American Menopause Society. https://www.menopause.org/publications/professional-publications/position-statements-other-reports **10.** Kingsberg SA, Kroll R, Goldstein I, et al. Patient acceptability and satisfaction with a low-dose solubilized vaginal estradiol softgel capsule, TX-004HR. *Menopause.* 2017;24(8):894-899. **11.** BIJUVA [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2021. **12.** Lobo RA, Archer DF, Kagan R, et al. A 17ß-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial. *Obstet Gynecol.* 2018;132(1):161-170. **13.** Lobo RA, Liu J, Stanczyk FZ, et al. Estradiol and progesterone bioavailability for moderate to severe vasomotor symptom treatment and endometrial protection with the continuous-combined regimen of TX-001HR (oral estradiol and progesterone capsules). *Menopause.* 2019;26(7):720-727. **14.** Sarrel P, Portman D, Lefebvre P, et al. Incremental direct and indirect costs of untreated vasomotor symptoms. *Menopause.* 2015;22(3):260-266. **15.** Simon JA, Kaunitz AM, Kroll R, Graham S, Bernick B, Mirkin S. Oral 17ß-estradiol/progesterone (TX-001HR) and quality of life in postmenopausal women with vasomotor symptoms. *Menopause.* 2019;26(5):506-512. **16.** Sussman M, Trocio J, Best C, et al. Prevalence of menopausal symptoms among mid-life women: findings from electronic medical records. *BMC Women's Health.* 2015;15:58-62. **17.** Kagan R, Constantine G, Kaunitz AM, Bernick B, Mirkin S. Improvement in sleep outcomes with a 17ß-estradiol-progesterone oral capsule (TX-001HR) for postmenopausal women. *Menopause.* 2018;25(6):622-628. **18.** Lobo RA, Kaunitz AM, Santoro N, et al. Metabolic and cardiovascular effects of TX-001HR in menopausal women with vasomotor symptoms. *Climacteric.* 2019;22(6):610-616. **19.** Archer DF, Pickar JH, Graham S, Constantine GD, Mirkin S. Effects of single-capsule 17ß-estradiol/progesterone (TX-001HR) on weight and blood pressure in postmenopausal women of the REPLENISH trial. Poster presented at: 2018 Annual Meeting of the North American Menopause Society, October 3-6, San Diego, CA. P-36.

BIJUVA® OR IMVEXXY® IS NOW A $15* COPAY FOR MOST INSURED, COVERED, ELIGIBLE PATIENTS

Most insured, covered, eligible patients may pay as little as $15 for a one month BIJUVA or IMVEXXY prescription

Patient Copay at Select Pharmacies**

Covered	Uncovered	Cash Pay
$15	$45	$45

Patient Copay at Retail Pharmacies†

Covered	Uncovered	Cash Pay
$35	$75	N/A

*Restrictions and limitations apply. Please see Terms, Conditions, and Eligibility Criteria. Out of Pocket cost may vary.

**Ask Mayne Pharma rep for more detail. No copay card required at select pharmacies

†At retail pharmacies, a copay card may be required to receive applicable savings

mayne pharma

NOT A LEAVE BEHIND. DO NOT DISTRIBUTE.