# AUSTRALIAN PI – BIJUVA® 1/100 (estradiol (as hemihydrate) and progesterone) SOFT CAPSULES

## WARNING

Estrogens and progestogens should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see Section 5.1 Pharmacodynamic properties– Clinical trials and Section 4.4 Special warnings and precautions for use).

The WHI study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated estrogens (0.625 mg) relative to placebo (see Section 5.1 Pharmacodynamic properties- Clinical trials and Section 4.4 Special warnings and precautions for use).

The Women's Health Initiative Memory Study (WHIMS), a sub-study of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 to 5.2 years of treatment with conjugated estrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (see Section 5.1 Pharmacodynamic properties – Clinical trials and Section 4.4 Special warnings and precautions for use).

Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestogens were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

## 1 NAME OF THE MEDICINE

Estradiol (as hemihydrate) and progesterone

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 1 mg of estradiol (as hemihydrate) and 100 mg of progesterone.

For the full list of excipients, see Section 6.1 List of excipients

## 3 PHARMACEUTICAL FORM

Soft capsule

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

Capsules are oval and approximately 5.2 – 6 mm in size.

# 4 CLINICAL PARTICULARS

## 4.1 Therapeutic indications

BIJUVA 1/100 is indicated for use during continuous combined hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women with an intact uterus and with at least 12 months since last menses.

## 4.2 Dose and method of administration

BIJUVA 1/100 is a combined HRT. The recommended oral dose for the initiation and continuation of treatment of postmenopausal symptoms should be the lowest effective dose, taken for the shortest duration (see also Section 4.4 Special warnings and precautions for use). Take one capsule each evening with food.

Continuous combined treatment may be started with BIJUVA 1/100 depending on the time since menopause and severity of symptoms. Women experiencing a natural menopause should commence treatment with BIJUVA 1/100 12 months after their last natural menstrual bleed. For surgically induced menopause, treatment may start immediately. Patients changing from a continuous sequential or cyclical preparation should complete the 28-day cycle and then change to BIJUVA 1/100.

***Management of missed capsules***

If a dose has been forgotten, it should be taken as soon as possible. If more than 12 hours have elapsed, treatment should be continued with the next capsule without taking the forgotten capsule. The likelihood of breakthrough bleeding or spotting may be increased.

***Special Patient Groups***

Patients changing from another continuous combined preparation may start therapy at any time.

BIJUVA 1/100 is not indicated for use in children.

Experience in treating women > 65 years with BIJUVA 1/100 is limited.

## 4.3 Contraindications

BIJUVA 1/100 is contradicted in patients with:

- known, past or suspected breast cancer;
- known or suspected estrogen-dependent malignant tumours (e.g., endometrial cancer);
- undiagnosed genital bleeding;
- untreated endometrial hyperplasia;
- previous or current venous thromboembolism (deep vein thrombosis, pulmonary embolism);
- known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency, see Section 4.4 Special warnings and precautions for use);
- active or recent arterial thromboembolic disease (e.g., angina, myocardial infarction);
- acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal;
- Porphyria;
- known hypersensitivity to the active substances or to any of the excipients.

## 4.4 Special warnings and precautions for use

General

BIJUVA 1/100 is indicated for the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually, and HRT should only be continued if the benefit outweighs the risk.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Identified precautions

***Medical Examination/follow up***

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see Breast cancer risk below). Investigations, including appropriate imaging tools, e.g., mammography, should be

carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

***Conditions Requiring Supervision***

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with BIJUVA 1/100, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumours, e.g., 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g., liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

***Reasons for Immediate Withdrawal of Therapy***

Therapy should be discontinued in cases where a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

***Endometrial Hyperplasia and Carcinoma***

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and estrogen dose (see Section 4.8 Endometrial cancer). After stopping treatment risk may remain elevated for at least 10 years.

The addition of a progestogen cyclically for at least 12 days per month/28-day cycle or continuous combined estrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with estrogen-only HRT.

Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

***Breast cancer***

The overall evidence shows an increased risk of breast cancer in women taking combined estrogen-progestogen or also estrogen-only HRT, that is dependent on the duration of taking HRT.

*Combined estrogen-progestogen therapy*

The randomised placebo-controlled trial the (Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see section 4.8 Breast cancer risk).

In a one year trial, among 1,684 women who received a combination of estradiol plus progesterone (1 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 50 mg progesterone or 0.25 mg estradiol plus 50 mg progesterone) or placebo (n=151), six new cases of breast cancer were diagnosed, two of which occurred among the group of 424 women treated with BIJUVA (estradiol and progesterone) capsules, 0.5 mg/100 mg, and two of which occurred among the group of 415 women treated with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg. No new cases of breast cancer were diagnosed in the group of 151 women treated with placebo.

*Estrogen-only therapy*

The WHI trial found no increase in the risk of breast cancer in hysterectomised women using estrogen-only HRT. Observational studies have mostly reported a small increase in risk of

having breast cancer diagnosed that is lower than that found in users of estrogen-progestogen combinations (see section 4.8 Breast cancer risk).

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

HRT, especially estrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

***Ovarian cancer***

Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies including the WHI trial suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see Section 4.8 Ovarian cancer).

***Venous thromboembolism***

HRT is associated with a 1.3-3-fold risk of developing venous thromboembolism (VTE), i.e., deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later.

Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3 Contraindications)

Generally recognised risk factors for VTE include, use of estrogens, older ages, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/ $m^2$), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g., antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk use of HRT.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnoea).

***Coronary artery disease (CAD)***

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestogen or estrogen-only HRT.

*Combined estrogen-progestogen therapy*

The relative risk of CAD during use of combined estrogen and progestogen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to estrogen and progestogen use is very low in healthy women close to menopause but will rise with more advanced age.

*Estrogen-only*

Randomised controlled data found no increased risk of CAD in hysterectomised women using estrogen-only therapy.

***Ischaemic stroke***

Combined estrogen-progestogen and estrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see Section 4.8 Risk of ischaemic stroke).

***Thyroid hormone levels***

Estrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels (by radioimmunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Serum concentrations of free T4 and T3 are unaltered. Other binding proteins may be elevated in serum, i.e., corticoid binding globulin (CBG), sex- hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

***Use in renal impairment***

Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition

***Use in the elderly***

Clinical experience is limited in patients above 65 years of age. HRT use does not improve cognitive function. There is some evidence of increased risk of developing dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.

***Paediatric use***

BIJUVA 1/100 is not indicated for use in paediatric populations, therefore, the safety and efficacy of estrogen and progesterone in patients under the age of 18 years have not been established.

***Effects on laboratory tests***

No formal studies on the effects on laboratory tests have been conducted with BIJUVA 1/100. The use of sex steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal, endocrine and renal function, plasma levels of (carrier) proteins, e.g., corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism, and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

## 4.5 Interactions with other medicines and other forms of interactions

No formal drug interaction studies have been conducted with BIJUVA 1/100. However, the drug-drug interactions of estradiol and progesterone have been extensively studied and are well established. Both estrogens and progesterone are metabolised via cytochrome P450 (CYP450).

***Effects of other medicinal products on BIJUVA 1/100***

The metabolism of estrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine) and e.g., rifampicin, rifabutin, nevirapine, efavirenz, and griseofulvin. Herbal preparations containing St John's Wort (Hypericum perforatum) may induce the metabolism of estrogens and progestogens.

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Clinically, an increased metabolism of estrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

Ketoconazole and other inhibitors of CYP450-3A4 may increase bioavailability of progesterone. Such interactions may increase the incidence of adverse effects such as nausea, breast tenderness, headaches associated with progesterone

***Effects of BIJUVA 1/100 on other medicinal products***

Hormone contraceptives containing estrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

Progesterone may raise the plasma concentration of ciclosporin.

## 4.6 Fertility, pregnancy and lactation

***Effects on fertility***

BIJUVA 1/100 is not indicated for use in women with childbearing potential.

***Use in pregnancy – Pregnancy Category D***

BIJUVA 1/100 is not indicated during pregnancy. If pregnancy occurs during medication with BIJUVA 1/100 treatment should be withdrawn immediately.

In animal studies, maternal administration of high doses of estrogens has produced urogenital malformations in the offspring. The relevance of these animal findings for the clinical use of estradiol is uncertain, but is considered likely to be low. Animal studies have also shown that high doses of progestogens can cause masculinisation of the female fetus.

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of estrogens and progestogens indicate no teratogenic or fetotoxic effect.

There are no adequate data from the use of estradiol/progesterone in pregnant women.

***Use in lactation.***

BIJUVA 1/100 is not indicated for use during lactation.

## 4.7 Effects on ability to drive and use machines

BIJUVA 1/100 does not affect the patient's ability to drive or operate machinery. Patients experiencing medicine-related symptoms should be advised not to drive or use machines until symptoms resolve completely.

## 4.8 Adverse effects (Undesirable effects)

Summary of the Safety Profile

The most reported related adverse drug reactions for BIJUVA 1/100 in clinical trials were breast tenderness (10.4%), headache (3.4%), nausea (2.2%), pelvic pain (3.1%), vaginal haemorrhage (3.4%), and vaginal discharge (3.4%).

**Table 1: Incidence of Related Treatment Emergent Adverse Events Occurring in ≥ 3% in 1 mg E2/100 mg P Treatment Arm and More Commonly than Placebo (Study TXC12 05)**

| | BIJUVA 1/100 1 mg E2/100 mg P (N=415) | Placebo (N=151) |
|---|---|---|
| **Breast tenderness** | 43 (10.4) | 1 (0.7) |
| **Headache** | 14 (3.4) | 1 (0.7) |
| **Nausea** | 9 (2.2) | 1 (0.7) |
| **Pelvic pain** | 13 (3.1) | 0 (0) |
| **Vaginal haemorrhage** | 14 (3.4) | 0 (0) |
| **Vaginal discharge** | 14 (3.4) | 1 (0.7) |

Source: TXC12-05 CSR, Table 43

Abbreviations: E2 - 17β-estradiol; P – progesterone

## Tabulated List of Adverse Reactions

### *Clinical trial data*

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

**Table 2: Details of the adverse reactions when taking BIJUVA 1/100.**

| MedDRA System Organ Class | Very common ≥ 1/10 | Common ≥ 1/100, < 1/10 | Uncommon ≥ 1/1,000, < 1/100 | Rare ≥ 1/10,000, < 1/1,000 |
|---|---|---|---|---|
| Blood and lymphatic system disorders | | | Anaemia, | |
| Ear and labyrinth disorders | | | Vertigo | |

BIJUVA® 1/100 (estradiol (as hemihydrate) and progesterone)

| **MedDRA System Organ Class** | **Very common ≥ 1/10** | **Common ≥ 1/100, < 1/10** | **Uncommon ≥ 1/1,000, < 1/100** | **Rare ≥ 1/10,000, < 1/1,000** |
|---|---|---|---|---|
| Endocrine disorders | | | Hirsutism | |
| Eye disorders | | | Visual impairment | |
| Gastrointestinal disorders | | Abdominal distension, Abdominal pain, Nausea | Abdominal discomfort, abdominal tenderness, Constipation, diarrhea, Dyspepsia, Hyperphagia, Dry mouth, oral discomfort, Vomiting, Dysgeusia, Flatulence<br><br>Pancreatitis acute | |
| General disorders and administration site conditions | | Fatigue | Chills | |
| Immune system disorders | | | Hypersensitivity | |
| Infections and infestations | | | Gastroenteritis, Furuncle, Vaginal infection, Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Otitis media acute | |
| Investigations | | Weight increased | Weight decreased, Prothrombin time prolonged, Protein S increased, Liver function test<br><br>abnormal, Blood pressure abnormal, blood fibrinogen | |

BIJUVA® 1/100 (estradiol (as hemihydrate) and progesterone)

| **MedDRA System Organ Class** | **Very common ≥ 1/10** | **Common ≥ 1/100, < 1/10** | **Uncommon ≥ 1/1,000, < 1/100** | **Rare ≥ 1/10,000, < 1/1,000** |
|---|---|---|---|---|
| | | | increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased, activated partial thromboplastin time prolonged | |
| Metabolism and nutrition disorders | | | Fluid retention, Hyperlipidemia, Hyperphagia Hyperuricemia | |
| Musculoskeletal and connective tissue disorders | | Back pain | Musculoskeletal pain, Pain in extremity, arthralgia, muscle spasms | |
| Neoplasms benign, malignant, and unspecified (incl cysts and polyps) | | | Breast cancer, adnexa uteri cyst | |
| Nervous system disorders | | Dizziness, Headache | Disturbance in attention, Memory impairment, Migraine with aura, Paraesthesia, Parosmia, Somnolence | |
| Psychiatric disorders | | | Sleep disorder, Abnormal dreams, Agitation, Anxiety, Depression, Insomnia, Irritability, Mood swings, Libido increased | |

BIJUVA® 1/100 (estradiol (as hemihydrate) and progesterone)

| **MedDRA System Organ Class** | **Very common ≥ 1/10** | **Common ≥ 1/100, < 1/10** | **Uncommon ≥ 1/1,000, < 1/100** | **Rare ≥ 1/10,000, < 1/1,000** |
|---|---|---|---|---|
| Reproductive system and breast disorders | Breast tenderness | Breast pain, pelvic pain, uterine pain/spasm, vaginal discharge, Vaginal bleeding haemorrhage | Breast disorders (calcification, discharge, discomfort, enlargement swelling, fibrocystic disease, nipple pain, benign breast neoplasm, Uterine/Cervical disorders (dysplasia, polyp, cyst, uterine haemorrhage, leiomyoma, uterine polyp, bleeding), Endometrial hypertrophy, abnormal biopsy, hot flush, metrorrhagia, post-menopausal haemorrhage, Vulvovaginal pruritus | |
| Skin and subcutaneous tissue disorders | | Acne, Alopecia | Dry skin, Pruritus, Rash, Telangiectasia | |
| Vascular disorders | | | Hypertension, Superficial thrombophlebitis | |

Breast cancer risk

An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestogen therapy for more than 5 years.

The increased risk in users of estrogen-only therapy is lower than that seen in users of estrogen-progestogen combinations.

The level of risk is dependent on the duration of use (see Section 4.4 Special warnings and precautions for use).

**Table 3: Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies (MWS).**

| **Age (years)**<br><br>**At start HRT** | **Incidence per 1000 never-users of HRT over a 5-year period*[1]**<br><br>**(50-54 years) *** | **Risk ratio** | **Additional cases per 1000 HRT users 5 years** |
|---|---|---|---|
| **Estrogen only HRT** | | | |
| 50 | 9-13.3 | 1.2 | 2.7 |
| **Combined estrogen-progestogen** | | | |
| 50-65 | 9-13.3 | 1.6 | 8 |

[1]*Taken from baseline incidence rates* in England in 2015 in women with BMI 27 (kg /m$^2$)

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

**Table 4: Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m$^2$)**

| **Age** (years)<br><br>**At start HRT** | **Incidence per 1000 never-users of HRT over a 10-year period (50-59 years) *** | **Risk Ratio** | **Additional cases per 1000 HRT users after 10 years** |
|---|---|---|---|
| | | **Estrogen only HRT** | |
| 50 | 26.6 | 1.3 | 7.1 |
| | | **Combined estrogen-progestogen** | |
| 50 | 26.6 | 1.8 | 20.8 |

*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m$^2$)

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately

**Table 5: US WHI studies - additional risk of breast cancer after 5 years' use**

| Age range (years) | Incidence per 1000 women in placebo arm over 5 years | Risk ratio & 95%CI | Additional cases per 1000 HRT users over 5 years (95%CI) |
|---|---|---|---|
| **CEE estrogen-only** | | | |
| 50-79 | 21 | 0.8 (0.7 – 1.0) | -4 (-6 – 0) *[2] |
| **CEE+MPA estrogen & progestogen‡** | | | |
| 50-79 | 17 | 1.2 (1.0 – 1.5) | +4 (0 – 9) |

[2]*WHI study in women with no uterus, which did not show an increase in risk of breast cancer*

‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Endometrial cancer

***Postmenopausal women with a uterus***

The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.

In women with a uterus, use of estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see Section 4.4 Special warnings and precautions for use). Depending on the duration of estrogen-only use and estrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 between the ages of 50 and 65.

Adding a progestogen to estrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (R.R of 1 .0 (0.8-1.2)).

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1 percent or less with BIJUVA 1/100 (estradiol and progesterone) capsules, 1 mg/100 mg (see Section 5.1 Pharmacodynamic properties).

Ovarian cancer

Use of estrogen-only or combined estrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4 Special warnings and precautions for use).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

***Risk of venous thromboembolism***

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e., deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see section 4.4 Special warnings and precautions for use). Results of the WHI studies are presented in Table 6.

**Table 6: Additional risk of VTE over 5 years' use**

| Age range (years) | Incidence per 1000 women in placebo arm over 5 years | Risk ratio and 95%CI | Additional cases per 1000 HRT users |
|---|---|---|---|
| **Oral estrogen-only*[3]** | | | |
| 50-59 | 7 | 1.2 (0.6-2.4) | 1 (-3 – 10) |
| **Oral combined estrogen-progestogen** | | | |
| 50-59 | 4 | 2.3 (1.2 – 4.3) | 5 (1 - 13) |

[3]Study in women with no uterus

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined estrogen-progestogen HRT over the age of 60 (see Section 4.4 Special warnings and precautions for use).

Risk of ischaemic stroke

The use of estrogen-only and estrogen + progestogen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see Section 4.4 Special warnings and precautions for use).

**Table 7 Additional risk of ischaemic stroke*4 over 5 years' use**

| Age range (years) | Incidence per 1000 women in placebo arm over 5 years | Risk ratio and 95%CI | Additional cases per 1000 HRT users |
|---|---|---|---|
| 50-59 | 8 | 1.3 (1.1-1.6) | 3 (1–5) |

[4]No differentiation was made between ischaemic and haemorrhagic stroke

Other adverse reactions

Other adverse effects have been reported in association with oestrogen/progestagen treatment:

- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see Section 4.4 Special warnings and precautions for use).

Reporting suspected adverse events

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

## 4.9 Overdose

There is little experience with overdose in human clinical trials. Both estradiol and progestogen are substances with low toxicity. Symptoms such as nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue, and withdrawal bleeding could occur in cases of overdosing. It is unlikely that any specific or symptomatic treatment will be necessary.

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

The ATC code is G03FA04 progesterone and estrogen

Mechanism of action

***Estradiol***

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of estrogen production in menopausal women and alleviates menopausal symptoms.

***Progesterone***

The active ingredient, progesterone is a natural progestogen, that is chemically and biologically identical to endogenous human progesterone. As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical trials

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

The evaluated co-primary efficacy endpoints included: 1) mean weekly reduction in frequency of moderate to severe vasomotor symptoms with BIJUVA 1/100 compared to placebo at Weeks 4 and 12; a clinically meaningful threshold for the reduction in frequency of vasomotor symptoms, defined as 14 vasomotor symptoms per week above placebo, was applied, and 2) mean weekly reduction in severity of moderate to severe vasomotor symptoms with BIJUVA 1/100 compared to placebo at Weeks 4 and 12.

Overall, BIJUVA 1/100 (estradiol and progesterone) capsules, 1 mg/100 mg, statistically significantly reduced both the frequency and severity of moderate to severe vasomotor symptoms from baseline compared with placebo at Weeks 4 and 12. A clinically meaningful threshold of a reduction of 14 vasomotor symptoms per week above placebo was not demonstrated for BIJUVA 1/100 (estradiol and progesterone) capsules, 1 mg/100 mg, until Week 5. The change from baseline in the frequency and severity of vasomotor symptoms observed and the difference from placebo are shown in Table 8 and Table 9, respectively.

**Table 8: Mean Weekly Change from Baseline and Difference from Placebo in the Frequency of Moderate to Severe Vasomotor Symptoms**

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

*Least square mean difference (SE) from placebo

**P-value of least square mean difference from placebo using mixed model repeated measures analyses

Definitions: SD – standard deviation; SE – standard error

**Table 9: Mean Weekly Change from Baseline and Difference from Placebo in the Severity of Moderate to Severe Vasomotor Symptoms**

| | **BIJUVA 1/100 1 mg/100 mg (N=141)** | **Placebo (N=135)** |
|---|---|---|
| **Week 4** | n = 134 | n = 126 |
| Baseline | 2.54 (0.325) | 2.52 (0.249) |
| Mean (SD) change from baseline | -0.48 (0.547) | -0.34 (0.386) |
| Difference from placebo* | -0.13 (0.061) | --- |
| P-value** | 0.031 | --- |
| | | |
| **Week 12** | n = 124 | n = 115 |
| Baseline | 2.55 (0.235) | 2.52 (0.245) |
| Mean (SD) change from baseline | -1.12 (0.963) | -0.56 (0.603) |
| Difference from placebo* | -0.57 (0.100) | --- |
| P-value** | <0.001 | --- |

*Least square mean difference (SE) from placebo

**P-value of least square mean difference from placebo using mixed model repeated measures analyses

Definitions: SD – standard deviation; SE – standard error

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

***Relief of oestrogen-deficiency symptoms and bleeding patterns***

Relief of menopausal symptoms was achieved during the first few weeks of treatment. In a 12-week study, 1 mg estradiol/100 mg progesterone significantly reduced the number and severity of hot flushes compared to placebo at Weeks 4 and 12.

In this study, amenorrhea was reported in 82.6% of the women who received 1 mg estradiol/ 100 mg progesterone during months 10 to 12. Bleeding and/or spotting was reported in the 1 mg estradiol/100 mg progesterone group by 30.1% of women during the first 3 months of treatment and by 17.4% of women during months 10 to 12.

***Endometrial safety***

The effects of 1 mg estradiol/100 mg progesterone (BIJUVA 1/100) on the endometrium was assessed in the 52-week safety trial. During the trial, assessments of endometrial biopsies taken at 12 months or at early trial discontinuation revealed 1 case of simple endometrial hyperplasia without atypia and no endometrial cancer in women who received BIJUVA 1/100 (1 mg estradiol/ 100 mg progesterone capsules (N=1/268, 0.37%; upper 2-sided 95% CI:1.83%).

Four (4) cases of disordered proliferative endometrium were also reported for BIJUVA 1/100 1 mg estradiol/100 mg progesterone) capsules.

**Table 10: Incidence of Endometrial Hyperplasia After up to 12 Months of Treatment**

| | **BIJUVA 1/100 1 mg /100 mg (N=268)** | **Placebo (N=85)** |
|---|---|---|
| **Hyperplasia Incidence (%)** | 1/268 (0.37) | 0/85 (0.00) |
| **Upper Two-sided 95% Confidence Interval** | 1.83% | 3.46% |

## 5.2 Pharmacokinetic properties

Absorption

The oral absorption of both estradiol and progesterone is subject to first pass metabolism.

***Food effect***

Concomitant food ingestion increased the extent of absorption (AUC) and peak plasma concentration ($C_{max}$) of the progesterone component of BIJUVA 1/100 relative to a fasting state when administered at a dose of 100 mg. Concomitant food ingestion had no effect on the AUC of the estradiol component of BIJUVA 1/100, but the rate of estradiol absorption was faster under fasting conditions compared to the fed state. Food increased the $C_{max}$ and AUC of the progesterone by 82% and 2.7-fold, respectively, relative to the fasting state.

After multiple doses of BIJUVA 1/100 (estradiol and progesterone) capsules, 1 mg/100 mg taken under fed conditions, the $t_{max}$ (the time at which the maximum concentration is attained) for estradiol is approximately 5 hours and approximately 3 hours for progesterone (See Table 11, below). Steady state for both estradiol and progesterone components of BIJUVA 1/100, as well as estradiol's main metabolite, estrone, is achieved within seven days.

Following repeat dosing with BIJUVA 1/100 (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 11: Mean (SD) Steady-State Pharmacokinetic Parameters after Administration of Capsules Containing 1 mg Estradiol/100 mg Progesterone in Healthy Postmenopausal Women (Fed conditions, Baseline Adjusted, at Day 7)**

| **Dosage Stre**ngth (estradiol/progesterone) | BIJUVA 1/100 (1 mg/100 mg)<br>**Mean (SD)** | |
|---|---|---|
| Estradiol | N | |
| $AUC_{0-\tau}$ (pg·h/mL) | 20 | 772.4 (384.1) |
| $C_{max}$ (pg/mL) | 20 | 42.27 (18.60) |
| $C_{avg}$ (pg/mL) | 19 | 33.99 (14.53) |
| $C_{trough}$ (pg/mL) | 20 | 28.63 (18.14) |
| $t_{max}$ (h) | 19 | 4.93(4.97) |
| $t_{½}$ (h)* | 19 | 26.47 (14.61) |
| Estrone | | |
| $AUC_{0-\tau}$ (pg·h/mL) | 20 | 4594 (2138) |
| $C_{max}$ (pg/mL) | 20 | 238.5 (100.4) |
| $C_{avg}$ (pg/mL) | 20 | 192.1 (89.43) |
| $C_{trough}$ (pg/mL) | 20 | 154.9 (81.42) |
| $t_{max}$ (h) | 20 | 5.45 (3.47) |
| $t_{½}$ (h)* | 19 | 22.37 (7.64) |
| Progesterone | | |
| $AUC_{0-\tau}$ (ng·h/mL) | 20 | 18.05 (15.58) |
| $C_{max}$ (ng/mL) | 20 | 11.31 (23.10) |
| $C_{avg}$ (ng/mL) | 20 | 0.76 (0.65) |
| $C_{trough}$ (ng/mL) | 20 | 0.17 (0.15) |
| $t_{max}$ (h) | 20 | 2.64 (1.51) |

BIJUVA® 1/100 (estradiol (as hemihydrate) and progesterone)

| **Dosage Stre**ngth (estradiol/progesterone) | BIJUVA 1/100 (1 mg/100 mg)<br>**Mean (SD)** | |
|---|---|---|
| $t_{½}$ (h) | 18 | 9.98 (2.57) |

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

***Estradiol***

Estradiol is extensively metabolised in the gastrointestinal mucosa during oral absorption and in the liver. Oral estradiol undergoes extensive first-pass metabolism in the liver and has an absolute bioavailability of 5% to 10% of the administered dose. Oral oestradiol exhibits dose-proportional pharmacokinetics over the dose range of up to 4 mg.

***Micronized progesterone***

Progesterone administered orally undergoes extensive first-pass metabolism in the liver. The absolute bioavailability of micronized progesterone is not known; the relative bioavailability of the oral progesterone compared with intramuscular progesterone is approximately 10%. Micronized progesterone exhibits dose proportional exhibited pharmacokinetics 100 and 300 mg.

Distribution

***Estradiol***

Estradiol is highly protein bound (approximately 95% to 98%), loosely to albumin or tightly to sex hormone-binding globulin, the major binding protein.

***Progesterone***

Progesterone is extensively bound to serum proteins (approximately 97%). About 17% of the circulating progesterone is bound with high affinity to transcortin (corticosteroid-binding globulin, CBG) and 80% with low affinity to albumin.

Metabolism

***Estradiol***

Estradiol undergoes rapid hepatic biotransformation and is converted primarily to estrone and estriol. There is a dynamic mutual conversion system between estradiol, estrone, and estrone sulfate and estradiol sulfate, which can be regarded as both metabolites and precursors. 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.

***Progesterone***

Progesterone is metabolised primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate conjugates.

Excretion

***Estradiol***

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

***Progesterone***

The glucuronide and sulfate conjugates of progesterone metabolites are eliminated in the urine.

## 5.3 Preclinical safety data

Genotoxicity

No genotoxicity studies have been conducted with combination of estradiol (hemihydrate)/progesterone.

There is limited evidence available in the literature suggesting that estradiol may be weakly genotoxic. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy and an increased incidence of sister chromatid exchanges (indicative of DNA damage) in mammalian cells. None of these effects were induced by estradiol in human lymphocyte cultures. Importantly, there was no evidence of clastogenicity in rodent bone marrow micronucleus assays.

Progesterone did not induce chromosomal aberrations or sister chromatid exchanges in cultured human cells nor chromosomal aberrations or DNA strand breaks in rodent cells. Progesterone did not induce dominant lethal mutations in mice or chromosomal aberrations in the bone marrow of rats *in vivo* although *in vivo* studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg. Weak clastogenic activity was found for progesterone in the rat hepatocyte micronucleus test after treatment with a high oral dose (100 mg/kg). Studies on transformation of rodent cells *in vitro* were inconclusive. Variable results were obtained in the mouse lymphoma tk assay. Progesterone was not mutagenic to bacteria.

Carcinogenicity

No carcinogenicity studies have been conducted with combination of estradiol (hemihydrate)/progesterone.

Long-term, continuous administration of natural and synthetic estrogens in laboratory animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. Carcinogenicity by estradiol may involve gene mutation induced by reactive metabolites or the activation of estrogen receptor-mediated signalling pathways that sustain the growth and survival of preneoplastic and malignant cells.

Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. Progesterone has been shown to induce/promote the formation of ovarian, uterine, mammary, and genital tract tumours in animals. The clinical relevance of these findings is unknown. Literature data provides no indication of potential carcinogenicity in humans.

When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumours and endometrial stromal sarcomas. In dogs, long-term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumours. Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumours in rats previously treated with a chemical carcinogen.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Mono and di-glycerides
Lauroyl macrogolglycerides
Gelatin
Hydrolysed gelatin
Glycerol
Opatint® Red DG-15001 (PI-141454)
Opatint® Concentrated Color Dispersion G-18006 (PI- 140158)
Opacode® WB water based Monogramming Ink NSP-78-18022 White (PI 3883)

## 6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the blister in the outer carton in order to protect from light.

### 6.5 Nature and contents of container

BIJUVA 1/100 is available in PVC/PE/PCTFE aluminium backed blister packs, containing 28 or 84 soft capsules.

Not all pack sizes may be marketed or available.

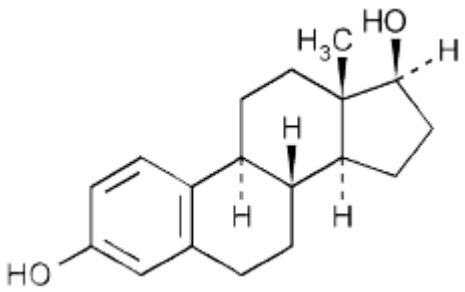
### 6.6 Special precautions for disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. The hormonal active compounds in the capsule may have harmful effects if it reaches the aquatic environment. In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

### 6.7 Physicochemical properties

Chemical Structure

***Estradiol hemihydrate***




Chemical name: estra-1,3,5(10)-triene-3,17β-diol (as hemihydrate). Estradiol has 5 chiral centres

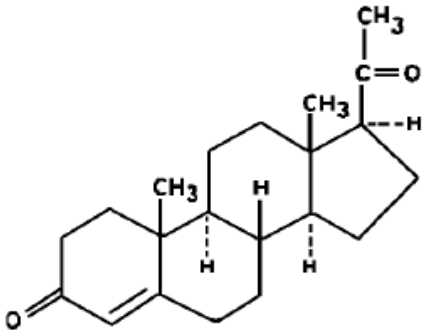
Molecular formula: $C_{18}H_{24}O_2$.

Molecular weight: 281.39

CAS number

Estradiol hemihydrate: 35380-71-3

***Progesterone***




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

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

Molecular weight: 314.5

CAS number

Progesterone: 57-83-0

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

# 8 SPONSOR

Theramex Australia Pty Ltd
Level 22, 60 Margaret Street,
Sydney NSW 2000

1800 THERAMEX or 1800 843 726

# 9 DATE OF FIRST APPROVAL

03/05/2022

# 10 DATE OF REVISION

N/A

**Attachment 1: Product information for AusPAR – Bijuva 1/100 - estradiol hemihydrate and progesterone - Theramex Australia Pty Ltd - PM-2021-02236-1-5 FINAL 17 February 2023. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-one>**



### 10.1 Summary table of changes

| Section Changed | Summary of new information |
|---|---|
| | |
| | |