Bijuve® (estradiol and progesterone)

Classification, cost and adverse event reporting information can be found on page 22 of this document.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bijuve 1mg/100mg Capsules, soft

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect: 0.042 mg Allura Red (E129).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, soft

Oval, opaque, light pink on one side and dark pink on the other side imprinted '1C1' with white ink.

Oval size approx. 7.4 mm x 14.2 mm..

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Continuous combined hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women with intact uterus and with at least 12 months since last menses.

The experience in treating women older than 65 years is limited.

4.2 Posology and method of administration

Posology

Bijuve is a combined HRT

The capsule should be taken every day without interruption.

Take one capsule each evening with food.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used.

Continuous combined treatment may be started with Bijuve depending on the time since menopause and severity of symptoms. Women experiencing a natural menopause should commence treatment with Bijuve 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 Bijuve.

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

Missed dose

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 tablet without taking the forgotten capsule. The likelihood of breakthrough bleeding or spotting may be increased.

Paediatric population

Bijuve is not indicated in children.

Method of administration

Oral

4.3 Contraindications

- Known, past or suspected breast cancer;

- Known or suspected oestrogen-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.);

- 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

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 as long as 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.

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' 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 which need 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 Bijuve, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen 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 oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). 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 oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-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 oestrogen-progestogen or also oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-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 oestrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see section 4.8).

Oestrogen-only therapy

The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-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 oestrogen-progestogen combinations (see section 4.8).

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 oestrogen-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 oestrogen-only or combined oestrogen-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).

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)

- Generally recognised risk factors for VTE include, use of oestrogens, older ages, major surgery, prolonged immobilisation, obesity (BMI>30 kg/m2), 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 oestrogen-progestogen or oestrogen-only HRT.

Combined oestrogen-progestogen therapy

The relative risk of CAD during use of combined oestrogen+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 oestrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Oestrogen-only

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

Ischaemic stroke

Combined oestrogen-progestogen and oestrogen-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).

Other conditions

- Oestrogens 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 oestrogen therapy in this condition.
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

- Oestrogens 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 radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased,

reflecting the elevated TBG. Free T4 and free T3 concentrations 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).

- HRT use does not improve cognitive function. There is some evidence of increased risk of possible dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

ALT elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvirwith and without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol,and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the following combination drug regimens ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. See section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interaction studies have been conducted with Bijuve

The drug-drug interactions of estradiol and progesterone have been extensively studied and are well established. Both estrogens and progesterone are metabolized via cytochrome P450

Effects of other medicinal products on Bijuve

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 oestrogens 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 Bijuve on other medicinal products

Progesterone may raise the plasma concentration of ciclosporin.

Effect of HRT with oestrogens on other medicinal products

Hormone contraceptives containing oestrogens 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.

Pharmacodynamic interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also with glecaprevir/pibretasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.

Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Bijuve is not indicated during pregnancy. If pregnancy occurs during medication with Bijuve treatment should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens and progestogens indicate no teratogenic or foetotoxic effect.

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

Lactation

Bijuve is not indicated during lactation.

Fertility

Bijuve is not indicated in women of childbearing potential.

4.7 Effects on ability to drive and use machines

Bijuve does not affect the ability to drive and use machines.

4.8 Undesirable Effects

a. Summary of the safety profile

The most commonly reported related adverse drug reactions for Bijuve in clinical trials were breast tenderness (10.4%), headache (3.4%), nausea (2.2%), pelvic pain (3.1%), vaginal hemorrhage (3.4%), and vaginal discharge (3.4%).

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)

	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

b. Tabulated list of adverse reaction

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.

The table below details the adverse reactions when taking Bijuve 1 mg/100 mg.

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	
Endocrine disorders			Hirsutism	
Eye disorders			Visual impairment	

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**
Gastrointestinal disorders		Abdominal distension, Abdominal pain, Nausea	Abdominal discomfort, abdominal tenderness, Constipation, diarrhea, Dyspepsia, Hyperphagia, Dry mouth, oral discomfort, Vomiting, Dysgeusia, Flatulence 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 abnormal, Blood pressure abnormal, blood fibrinogen increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase	

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, 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, Paresthesia, Parosmia, Somnolence	
Psychiatric disorders			Sleep disorder, Abnormal dreams, Agitation, Anxiety, Depression, Insomnia, Irritability, Mood swings, Libido increased	
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	

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**
			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 oestrogen-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).

• 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) are presented.

– Largest meta-analysis of prospective epidemiological stud**ies Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m2)**

Age **at start HRT** (years)	Incidence per 1000 never-users of HRT over a 5 year period*[1] **(50-54 years)***	Risk ratio	Additional cases per 1000 HRT users 5 years
Oestrogen only HRT			
50	9-13.3	1.2	2.7
Combined oestrogen-progestogen			
50-65	9-13.3	1.6	8
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

[1]*Taken from baseline incidence rates* in England in 2015 in women with BMI 27 (kg/m2)

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m2)

Age at start HRT **(years)**	**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**
		Oestrogen only HRT	
50	*26.6*	*1.3*	*7.1*
		Combined oestrogen-progestagen	
50	*26.6*	*1.8*	*20.8*

*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m2)

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

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 oestrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*[2]
CEE+MPA oestrogen & 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 oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4). Depending on the duration of oestrogen-only use and oestrogen 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 oestrogen-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)).

Ovarian cancer

Use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).

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 HT (see section 4.4.). Results of the WHI studies are presented:

WHI Studies - 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 oestrogen-only*[3]			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined oestrogen-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).

Risk of ischaemic stroke

• The use of oestrogen-only and oestrogen + 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.

WHI studies combined - 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 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the via the national reporting system listed in Appendix V.

4.9 Overdose

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.

Aforementioned information is applicable for overdosing by children as well.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The ATC code is G03FA04 progesterone and oestrogen

Estradiol

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen 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 oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical efficacy and safety

Bijuve (1 mg estradiol/100 mg progesterone) was evaluated in 726 postmenopausal women who participated in 1 phase 3 trial. Among these, 141 women were treated with 1 mg estradiol/100 mg progesterone and 135 received placebo. Endometrial safety was evaluated in 268 women for a period of 1 year.

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, 1mg 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 1mg estradiol/ 100 mg progesterone during months 10 to 12. Bleeding and/or spotting was reported in the 1mg 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 1mg estradiol/100 mg progesterone (Bijuve) 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 Bijuve (1 mg estradiol/ 100 mg progesterone capsules (N=1/268, 0.37%; 2-sided 95% CI:1.83%).

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

5.2 Pharmacokinetic properties

Absorption

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

Food Effect

Concomitant food ingestion increased the extent of absorption (AUC) and peak plasma concentration (Cmax) of the progesterone component of Bijuve 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 Bijuve, but the rate of estradiol absorption was faster under fasting conditions compared to the fed state. Food increased the Cmax and AUC of the progesterone by 82% and 2.7-fold, respectively, relative to the fasting state.

After multiple doses of Bijuve (estradiol and progesterone) capsules, 1 mg/100 mg **taken under fed conditions**, the tmax (the time at which the maximum concentration is attained) for estradiol is approximately 5 hours and approximately 3 hours for progesterone (See Table 2, below). Steady state for both estradiol and progesterone components of Bijuve, as well as estradiol's main metabolite, estrone, is achieved within seven days.

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 Strength (estradiol/progesterone)	Bijuve 1 mg/100 mg Mean (SD)	
Estradiol	N	
$AUC_{0-\tau}$ (pg·h/mL)	20	772.4 (384.1)
C_{max} (pg/mL)	20	42.27 (18.60)
C_{avg} (pg/mL)	19	33.99 (14.53)
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)

Dosage Strength (estradiol/progesterone)	Bijuve 1 mg/100 mg Mean (SD)	
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)
$t_{½}$ (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 metabolized 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 transcortine and 80% with low affinity to albumin.

Elimination

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

Metabolism

Estradiol

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. Oestrogens 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 metabolized 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

There are no preclinical safety data of relevance to the prescriber in the target population that are additional to those already included in other sections of the Summary of Product Characteristics (SmPC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content contains:

Medium chain mono/diglycerides

Lauroyl Macrogolglycerides 32

Capsule shell contains:

Gelatin, 200 Bloom

Hydrolyzed gelatin

Glycerin (E422)

Allura Red (E129)

Titanium Dioxide (E171)

Printing ink (Opacode® White WB) contains:

Propylene glycol (E1520)

Titanium dioxide (E171)

Polyvinyl acetate phthalate

Polyethylene glycol (E1521)

Ammonium hydroxide (E527)

6.2 Incompatibilities

None

6.3 Shelf life

2 years

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

PVC/PE/PCTFE – Aluminium blisters of 28 or 84 soft gelatin capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Bijuve capsules no longer required should not be disposed via wastewater or the municipal sewage system. The hormonal active compounds in the capsule may have harmful effects if reaching the aquatic environment. The capsules should be returned to a pharmacy or disposed of in another safe way according to local requirements. These measures will help to protect the environment.

7. MARKETING AUTHORISATION HOLDER

Theramex Ireland Ltd

3rd Floor, Kilmore House,

Park Lane,

Spencer Dock,

Dublin 1

D01 YE64,

Ireland

8. MARKETING AUTHORISATION NUMBER(S)

PL 49876/0015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/02/2021

10. DATE OF REVISION OF THE TEXT

06/05/2025

Legal classification: Prescription only medicine (POM)

Bijuve® (estradiol and progesterone) Package Quantities & Cost: 28 x capsules £8.14

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellowcard in the Google Play or Apple App store. Adverse events should also be reported to Theramex on medinfo.uk@theramex.com or Tel: 0044(0)333 0096795