**SCHEDULING STATUS**
S4

## 1. NAME OF THE MEDICINE
**BIJUVA,** 1 mg/100 mg soft gel capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each soft gel capsule contains 1 mg estradiol (as estradiol hemihydrate) and 100 mg progesterone.

*Excipients with known effect:*
0,042 mg Allura Red (E129).

Sugar free.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM
Soft gel capsules.

Oval, opaque, light pink on one side and dark pink on the other side imprinted '1C1' with white ink. Oval size approx. 5,2 – 6 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**
**BIJUVA** 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 section 4.4) should be used.

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

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***
**BIJUVA** is not indicated in children.

**Method of administration**
Oral

**4.3 Contraindications**
- Known hypersensitivity to the active substances or to any of the excipients (see section 6.1).
- 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 (see section 4.4).
- Porphyria.

**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 **BIJUVA**, 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/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 medicine 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 oestrogen 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.
- 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 radioimmunoassay) or T3 levels (by radioimmunoassay). 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.

**4.5 Interaction with other medicines and other forms of interaction**
No drug-drug interaction studies have been conducted with **BIJUVA**.

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

**Effects of other medicines on BIJUVA**
The metabolism of oestrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbitone, 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 oestrogens 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 on other medicines**
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 medicines together.

Progesterone may raise the plasma concentration of ciclosporin.

**4.6 Fertility, pregnancy and lactation**
**Pregnancy**
**BIJUVA** is not indicated during pregnancy. If pregnancy occurs during medication with **BIJUVA** 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 fetotoxic effect.

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

**Lactation**
**BIJUVA** is not indicated during lactation.

**Fertility**
**BIJUVA** is not indicated in women of childbearing potential.

**4.7 Effects on ability to drive and use machines**
**BIJUVA** can cause side effects, such as dizziness, vertigo, visual impairment or fatigue. Patients should be advised that if they experience any of these symptoms they should not to drive or operate machinery.

**4.8 Undesirable effects**
**a. Summary of the safety profile**
The most commonly reported related adverse drug reactions for **BIJUVA** 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 %).

Incidence of Related Treatment Emergent Adverse Events Occurring in ≥ 3 % in 1 mg estradiol/100 mg progesterone Treatment Arm and More Commonly than Placebo (Study TXC12-05)

| **Adverse Event** | **1 mg estradiol / 100 mg progesterone (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) |

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 (1 684 were treated with estradiol and progesterone capsules once daily and 151 women received placebo. Most women (~ 70 %) in the active treatment groups were treated for ≥ 326 days.

**The table below details the adverse reactions when taking BIJUVA 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** |
|---|---|---|---|---|
| Infections and infestations | | | Gastroenteritis, furuncle, vaginal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, otitis media acute | |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | | | Breast cancer, adnexa uteri cyst | |
| Blood and lymphatic system disorders | | | Anaemia | |
| Immune system disorders | | | Hypersensitivity | |
| Endocrine disorders | | | Hirsutism | |
| Metabolism and nutrition disorders | | | Fluid retention, hyperlipidaemia, hyperphagia, hyperuricemia | |
| Psychiatric disorders | | | Sleep disorder, abnormal dreams, agitation, anxiety, depression, insomnia, irritability, mood swings, increased libido | |
| Nervous system disorders | | Dizziness, headache | Disturbance in attention, memory impairment, migraine with aura, paraesthesia, | |

| | | | | |
|---|---|---|---|---|
| | | | parasosmnia, somnolence | |
| Eye disorders | | | Visual impairment | |
| Ear and labyrinth disorders | | | Vertigo | |
| Vascular disorders | | | Hypertension, superficial thrombophlebitis | |
| Gastrointestinal disorders | | Abdominal distension, abdominal pain, nausea | Abdominal discomfort, abdominal tenderness, constipation, diarrhoea, dyspepsia, hyperphagia, dry mouth, oral discomfort, vomiting, dysgeusia, flatulence, acute pancreatitis | |
| Skin and subcutaneous tissue disorders | | Acne, alopecia | Dry skin, pruritus, rash, telangiectasia | |
| Musculoskeletal and connective tissue disorders | | Back pain | Musculoskeletal pain, pain in extremity, arthralgia, muscle spasms | |
| 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 | |
| General disorders and administration site conditions | | Fatigue | Chills | |
| Investigations | | Increased weight | Decreased weight, prolonged prothrombin time, increased protein S, abnormal liver function test, abnormal blood pressure, increased blood fibrinogen, increased blood alkaline phosphatase, increased aspartate aminotransferase, increased alanine aminotransferase, prolonged activated partial thromboplastin time | |

***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 oestrogen-only therapy is lower than that seen in users of oestrogen-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 studies Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m$^2$)**

| **Age at start HRT (years)** | **Incidence per 1 000 never-users of HRT over a 5 year period*[1] (50 – 54 years)*** | **Risk ratio (RR)** | **Additional cases per 1 000 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/m$^2$).*

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

| **Age at start HRT (years)** | **Incidence per 1 000 never-users of HRT over a 10 year period (50 – 59 years)*** | **Risk Ratio** | **Additional cases per 1 000 HRT users after 10 years** |
|---|---|---|---|
| | | *Oestrogen only HRT* | |
| 50 | 26,6 | 1,3 | 7,1 |
| | | *Combined oestrogen-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.

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

| **Age range (years)** | **Incidence per 1 000 women in placebo arm over 5 years** | **Risk ratio & 95 % CI** | **Additional cases per 1 000 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 1 000 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 1 000 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 (RR 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 2 000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 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 1 000 women in placebo arm over 5 years** | **Risk ratio and 95 % CI** | **Additional cases per 1 000 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 oestrogen-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 1 000 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/progestogen 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 **BIJUVA** is important. It allows continued monitoring of the benefit/risk balance of **BIJUVA**. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

**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

Category and class: A 21.8.2 Progesterone with or without oestrogens
Pharmacotherapeutic group: progesterone and oestrogen
ATC code: G03FA04

**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**
**BIJUVA** (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 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**) on the endometrium were 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 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 **BIJUVA** (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 metabolism.

***Food Effect***
Concomitant food ingestion increased the extent of absorption (AUC) and peak plasma concentration ($C_{max}$) of the progesterone component of **BIJUVA** 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**, 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** (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 2, below). Steady state for both estradiol and progesterone components of **BIJUVA**, as well as the main metabolite of estradiol, 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)** | **BIJUVA 1 mg/100 mg** |
|---|---|
| **Estradiol** | **Mean (SD)** |
| $AUC_{0-\tau}$ (pg·h/mL) | 772,4 (384,1) |
| $C_{max}$ (pg/mL) | 42,27 (18,60) |
| $C_{avg}$ (pg/mL) | 33,99 (14,53) |
| $C_{trough}$ (pg/mL) | 28,63 (18,14) |
| $t_{max}$ (h) | 4,93 (4,97) |
| $t_{½}$ (h)* | 26,47 (14,61) |
| **Estrone** | **Mean (SD)** |
| $AUC_{0-\tau}$ (pg·h/mL) | 4594 (2138) |
| $C_{max}$ (pg/mL) | 238,5 (100,4) |
| $C_{avg}$ (pg/mL) | 192,1 (89,43) |
| $C_{trough}$ (pg/mL) | 154,9 (81,42) |
| $t_{max}$ (h) | 5,45 (3,47) |
| $t_{½}$ (h)* | 22,37 (7,64) |
| **Progesterone** | **Mean (SD)** |
| $AUC_{0-\tau}$ (ng·h/mL) | 18,05 (15,58) |
| $C_{max}$ (ng/mL) | 11,31 (23,10) |
| $C_{avg}$ (ng/mL) | 0,76 (0,65) |
| $C_{trough}$ (ng/mL) | 0,17 (0,15) |
| $t_{max}$ (h) | 2,64 (1,51) |
| $t_{½}$ (h) | 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 estradiol exhibits dose-proportional pharmacokinetics over the dose range of up to 4 mg.

***Micronised progesterone***
Progesterone administered orally undergoes extensive first-pass metabolism in the liver. The absolute bioavailability of micronised progesterone is not known; the relative bioavailability of the oral progesterone compared with intramuscular progesterone is approximately 10 %. Micronised 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 and 80 % with low affinity to albumin.

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

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

**Elimination**
***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.

**6. PHARMACEUTICAL PARTICULARS**
**6.1 List of excipients**
*Capsule content contains:*
Medium chain mono/diglycerides

Lauroyl macrogolglycerides 32
*Capsule shell contains:*
Gelatine (200 Bloom)
Hydrolysed gelatine
Glycerin (E422)
Allura Red (E129) (colourant)
Titanium dioxide (E171) (colourant)

*Printing ink (Opacode® White WB) contains:*
Propylene glycol (E1520)
Titanium dioxide (E171) (colourant)
Polyvinyl acetate phthalate
Polyethylene glycol (E1521)
Ammonium hydroxide (E527)

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
2 years

**6.4 Special precautions for storage**
Store at or below 25 °C.
Keep the blister in the outer carton to protect from light.

**6.5 Nature and contents of container**
Clear PVC/PE/PCTFE/aluminium blister strips in an outer carton.
Pack sizes: 28 or 84 soft gelatine capsules.
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**
**BIJUVA** 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. HOLDER OF CERTIFICATE OF REGISTRATION**
Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

**8. REGISTRATION NUMBER**
57/21.8.2/0075

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
06 May 2025

**10. DATE OF REVISION OF THE TEXT**

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