New Medicine Assessment

Estradiol (as estradiol hemihydrate) and progesterone 1mg/100mg Soft Capsules (Bijuve®)

For 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

Recommendation: Green (Restricted)

Estradiol (as estradiol hemihydrate) and progesterone 1mg/100mg Soft Capsules (Bijuve®) for continuous combined hormone replacement therapy (HRT) is recommended for initiation and ongoing prescribing in both primary and secondary care provided that:

- Bijuve® is an alternative when other HRT treatments have not been tolerated or when Femoston-Conti® is being considered **OR**
- Bijuve® replaces HRT regimens where separate oestrogen and micronised progesterone are used (single hormone products used in combination are more expensive than Bijuve®).

Summary of supporting evidence:

- NICE recommends prescribing progesterone alongside oestrogen HRT in menopausal women with a uterus.
- Bijuve® is accepted for use within NHS Scotland. Bijuve® offers an additional treatment choice of continuous combined hormone replacement therapy. [10]
- Bijuve® may provide a better option for some patients, especially with the convenience of using one tablet rather than taking estradiol and micronised progesterone separately. [9]
- In addition, it would provide more options in terms of dosing for those who don't tolerate micronised progesterone at higher doses [9]
- Evidence from large observational studies and case-controlled studies suggests that micronised progesterone and dydrogesterone are unlikely to increase the risk of venous thrombosis and are associated with a lower risk of breast cancer compared to that noted with oral progestogens. [11]
- Micronised progesterone compared favourably with MPA with respect to bleeding patterns and lipid metabolism.
- Micronised progesterone or dydrogesterone may be preferred in women with hypertriglyceridaemia due to their neutral effect on lipid profile.
- Bijuve® is more expensive than a number of alternative non-bioidentical hormone therapies.

Date: December 2022

Details of Review

Name of medicine (generic & brand name)**:** Estradiol (as estradiol hemihydrate) and progesterone (Bijuve®)

Strength(s) and form(s): Estradiol (as estradiol hemihydrate) and progesterone 1mg/100mg Soft Capsules

Dose and administration: The capsule should be taken every day without interruption.

Take one capsule each evening with food. [1]

BNF therapeutic class / mode of action: Oestrogens and HRT

Licensed indication(s):

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. [1]

Proposed use (if different from, or in addition to, licensed indication above):N/A

Course and cost: 28 X Capsules = £8.14; Annual cost = £106

Current standard of care/comparator therapies:

- Kliovance® tablets: 84 X Tablets = £13.20; Annual cost = £57
- Premique Low Dose®: 84 X Tables = £6.52; Annual cost = £28
- Evorel Conti® transdermal patch: 24 X Patches = £37.22; Annual cost = £161

Relevant NICE guidance:

[NG23] Menopause: Diagnosis and Management [2]

- Vasomotor symptoms:

- 1.4.2 Offer women HRT for vasomotor symptoms after discussing with them the short-term (up to 5 years) and longer-term benefits and risks. Offer oestrogen and progestogen to women with a uterus.

- 1.4.5 Consider HRT to alleviate low mood that arises as a result of the menopause.

[QS143] Menopause [3]

- Quality statement 4: Reviewing treatments for menopausal symptoms
- Women having treatment for menopausal symptoms have a review 3 months after starting each treatment and then at least annually.

NICE CKS [4]

Women vary in their tolerance to progestogens and changing the progestogen component of combined HRT may be needed if progestogenic adverse effects occur.

Progestogen-related adverse effects include:

Fluid retention, breast tenderness, headaches or migraine, mood swings, premenstrual

syndrome-like symptoms, depression, acne vulgaris, lower abdominal pain, and back pain. They tend to occur in a cyclical pattern during the progestogen phase of cyclical HRT.

Micronized progesterone or dydrogesterone may be preferred in women with hypertriglyceridaemia due to their neutral effect on lipid profile.

Background and context

There are more than 11 million women over the age of 45 in the UK according to the Office of National Statistics 2011 census. This number has been steadily increasing and is forecast to continue to rise. The associated increase in the number of women going through the menopause is expected to result in more GP consultations and more new referrals to secondary care of women needing short-term symptom control and those who have associated long-term health issues.

Menopause is a biological stage in a woman's life when she is no longer fertile and is marked by the cessation of menstruation. A woman is defined as postmenopausal from 1 year after her last period. The changes associated with menopause and the perimenopause (the years leading up to the menopause) occur when ovarian function diminishes and ceases. This includes the cessation of both egg (oocyte) maturation and sex hormone (principally oestrogen and progesterone) secretion. [2]

A woman with a uterus normally requires oestrogen with cyclical progestogen for the last 12 to 14 days of the cycle or a preparation which involves continuous administration of an oestrogen and a progestogen (or one which provides both oestrogenic and progestogenic activity in a single preparation). Continuous combined preparations or tibolone are **not suitable** for use in the perimenopause or within 12 months of the last menstrual period; women who use such preparations may bleed irregularly in the early stages of treatment—if bleeding continues endometrial abnormality should be ruled out and consideration given to changing to cyclical HRT. [5]

Progestogen administration is required to oppose naturally produced or administered oestrogens to provide endometrial protection. Within HRT regimens, this should be delivered for at least the same duration as that produced during the luteal phase of the monthly cycle and in the recommended doses to protect against the risk of endometrial hyperplasia and endometrial cancer. [6]

Summary of evidence

Summary of efficacy data in proposed use:

REPLENISH Trial [7]

A single major trial was conducted to evaluate the efficacy and safety of a single-capsule 17β-estradiol-progesterone (Bijuve®). REPLENISH was a phase III, 12-month, randomized, double-blind, placebo-controlled, multicenter trial. Women (aged 40–65 years) with vasomotor symptoms and a uterus were randomized to daily estradiol (mg)– progesterone (mg) (1/100, 0.5/100, 0.5/50, or 0.25/50), and women in the vasomotor symptoms substudy (women with moderate-to-severe hot flushes [seven or greater per day or 50 or greater per week]) to the same estradiol–progesterone doses or placebo. The primary safety endpoint was endometrial hyperplasia incidence at 12 months in all women (the total population), and the primary efficacy endpoints were frequency and severity changes (from daily diaries) in moderate-to-severe vasomotor symptoms with estradiol– progesterone compared with placebo at weeks 4 and 12 in the vasomotor symptoms substudy. A sample size of 250 women in each active treatment arm with two or less endometrial hyperplasia cases would result in 1% or less annual incidence (upper bound 2.5% or less, one-sided 95% CI).

One thousand eight hundred forty-five women were enrolled and randomized from August 2013 to October 2015; 1,835 received medication (safety population); 1,255 were eligible for the endometrial safety population; 726 comprised the vasomotor symptoms substudy. No endometrial hyperplasia was found. Frequency and severity of vasomotor symptoms significantly decreased

from baseline with 1 mg estradiol and 100 mg progesterone and 0.5 mg estradiol and 100 mg progesterone compared with placebo at week 4 (frequency: by 40.6 and 35.1 points [1 mg and 100 mg and 0.5 mg and 100 mg, respectively] vs 26.4 points [placebo]; severity: by 0.48 and 0.51 vs 0.34 points) and week 12 (by 55.1 and 53.7 vs 40.2; severity: by 1.12 and 0.90 vs 0.56); 0.5 mg estradiol and 50 mg progesterone improved (P<0.05) frequency and severity at week 12, and 0.25 mg estradiol and 50 mg progesterone frequency but not severity at weeks 4 and 12.

Cochrane Review 2016 [8]

This Cochrane review intended to determine the effectiveness and safety of bioidentical hormones compared to placebo or non-bioidentical hormones for the relief of vasomotor symptoms. The authors identified 23 RCTs (n=5779). Most studies (20/23) included only women with moderate to severe hot flushes. All studies compared unopposed 17 beta-estradiol (beta-estradiol) versus placebo or conjugated equine oestrogens (CEE).

There was low to moderate quality evidence that bioidentical hormone therapy (BHT) in various forms and doses is more effective than placebo for treating moderate to severe menopausal hot flushes. There was low to moderate quality evidence of higher rates of adverse effects such as headache, vaginal bleeding, breast tenderness and skin reactions in the BHT group. There was some evidence to suggest that higher doses of BHT are associated with greater effectiveness but also with higher risk of adverse effects.

There was no good evidence of a difference in effectiveness between BHT and CEE, and findings with regard to adverse effects were inconsistent. The quality of the evidence was too low to reach any firm conclusions.

Summary of safety data:

The safety population (N = 1,835) included randomized patients from the VMS substudy population and the non-substudy population (i.e., the overall study population) who took at least one dose of medication. All patients randomized to active treatment who completed 12 treatment months and had evaluable baseline and 12-month biopsies) were also assessed for endometrial hyperplasia. [9]

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 haemorrhage (3.4%), and vaginal discharge (3.4%). [1]

The full list of adverse reactions listed in the SPC is detailed below:

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

The SPC contains warning relating to the increased risk of breast, endometrial, and ovarian cancer in women using oestrogen containing HRT. There are also warnings about increased risk of ischaemic stroke and venous thromboembolism in patients using combined oestrogen-progestogen HRT.

Bijuve® is contraindicated in patients with:

- 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;
- 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.

Strengths and limitations of the evidence:

Strengths

- NICE recommends prescribing progesterone alongside oestrogen HRT in menopausal women with a uterus.
- Bijuve® is accepted for use within NHS Scotland. Bijuve® offers an additional treatment choice of continuous combined hormone replacement therapy. [10]
- Bijuve® may provide a better option for some patients, especially with the convenience of using one tablet rather than taking estradiol and micronised progesterone separately. [9]
- In addition, it would provide more options in terms of dosing for those who don't tolerate micronised progesterone at higher doses [9]
- Evidence from large observational studies and case-controlled studies suggests that micronised progesterone and dydrogesterone are unlikely to increase the risk of venous thrombosis and are associated with a lower risk of breast cancer compared to that noted with oral progestogens. [11]
- Micronised progesterone compared favourably with MPA with respect to bleeding patterns and lipid metabolism. [11]
- Micronised progesterone or dydrogesterone may be preferred in women with hypertriglyceridaemia due to their neutral effect on lipid profile. [9]

Limitations

- A Cochrane review found that there was no good evidence of a difference in effectiveness between bioidentical hormone therapy (BHT) and conjugated equine estrogen (CEE), and findings with regard to adverse effects were inconsistent. The quality of the evidence was too low to reach any firm conclusions. [8]
- Bijuve® is more expensive than a number of alternative non-bioidentical hormone therapies.
- Bijuve® has not been compared to other HRT products. The REPLENISH study only compared Bijuve® to placebo.
- Bioidentical oestrogen does not appear to have additional benefits relative to comparable oestrogen containing HRT products.

Summary of evidence on cost effectiveness:

N/A

Prescribing and risk management issues:

MHRA Drug Safety Update (2019): Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping. [12] MHRA Drug Safety Update (2014): Hormone-replacement therapy: updated advice. [13]

Commissioning considerations:

Innovation, need and equity implications of the intervention:
Body identical progesterone has a lower risk of breast cancer compared with synthetic alternatives and has a neutral effect on blood clotting and blood lipids like cholesterol.
Financial implications of the intervention:
Bijuve® capsules are between £49-£78 more expensive per patient per year compared to comparator therapies (see section above) and is the same price as Femoston-Conti®. If Bijuve® is prescribed in line with the recommendations in this review as an alternative to current options when Femoston-Conti® is being considered or to replace HRT regimens where separate oestrogen and micronised progesterone are used (single hormone products used in combination are more expensive than Bijuve®). It would be expected that adding Bijuve® to the already available HRT treatment options would be cost-neutral.
Service Impact Issues Identified:
No service impact is expected as this product would be available as an alternative treatment option.
Equality and Inclusion Issues Identified:
See the separate EIRA form.
Cross Border Issues Identified:
GMMMG does not have a commissioning position for Bijuve® and Pan Mersey APC has assigned Bijuve® a Grey RAG status (not recommended until a review has taken place).
Legal Issues Identified:
None identified.
Media/ Public Interest:

There has been significant media attention about the provision of HRT therapy and Bijuve® has received endorsement by a celebrity.

References

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[2] National Institute for Health and Care Excellence, "Menopause: Diagnosis and Management NG23," Nov 2015. [Online]. Available: https://www.nice.org.uk/guidance/ng23. [Accessed December 2022].

[3] National Institute for Health and Care Excellence, "NICE Quality Standard 143 Menopause," February 2017. [Online]. Available: https://www.nice.org.uk/guidance/qs143. [Accessed December 2022].

[4] National Institute for Health and Care Excellence, "NICE CKS: Menopause," November 2020. [Online]. Available: https://www.nice.org.uk/guidance/qs143. [Accessed December 2022].

[5] British National Formulary, "Sex Hormones," [Online]. Available: https://bnf.nice.org.uk/treatment-summary/sex-hormones.html.

[6] British Menopause Society, "Progestogens and endometrial protection," October 2021. [Online]. [Accessed December 2022].

[7] RA Lobo et al, "A 17b-Estradiol–Progesterone Oral Capsule for Vasomotor Symptoms in Postmenopausal Women: A Randomized Controlled Trial," *Obstetrics and Gynecology,* vol. 132, no. 1, pp. 161-170, 2018.

[8] AMIS Gaudard et al, "Bioidentical hormones for women with vasomotor symptoms (Review)," *Cochrane Database of Systematic Reviews,* no. 8, p. CD010407, 2016.

[9] The Canadian Agency for Drugs and Technologies in Health (CADTH), "CADTH Reimbursement Review Estradiol and Progesterone (BIJUVA)," *Canadian Journal of Health Technologies,* vol. 2, no. 4, 2022.

[10] Scottish Medicines Consortium, "Estradiol / micronised progesterone (Bijuve)," August 2022. [Online]. Available: https://www.scottishmedicines.org.uk/media/7098/estradiol-micronised-progesterone-bijuve-abb-final-aug-2022-for-website.pdf. [Accessed December 2022].

[11] British Menopause Society, "BMS & WHC's 2020 recommendations on hormone replacement therapy in menopausal women," March 2021. [Online]. Available: thebms.org.uk/publications/consensus-statements/bms-whcs-2020-recommendations-on-hormone-replacement-therapy-in-menopausal-

women. [Accessed December 2022].

[12] Medicines and Healthcare products Regulatory Agency, "Hormone replacement therapy (HRT): further information on the known increased risk of breast cancer with HRT and its persistence after stopping," 2019. [Online]. Available: https://www.gov.uk/drug-safety-update/hormone-replacement-therapy-hrt-further-information-on-the-known-increased-risk-of-breast-cancer-with-hrt-and-its-persistence-after-stopping. [Accessed December 2022].

[13] Medicines and Healthcare products Regulatory Agency, "Hormone-replacement therapy - updated advice," December 2014. [Online]. Available: https://www.gov.uk/drug-safety-update/hormone-replacement-therapy-updated-advice. [Accessed December 2022].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Produced by:

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