Application and Case for Introduction of New Medicine Service Developments

Application for: Bijuve® (Estradiol 1mg / micronised progesterone 100mg). Indicated for continuous combined hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women with intact uterus and with at least 12 months since last menses.

Purpose of this form: for providers to apply to commissioners for in-year funding of any new drug or extended use of an existing drug (e.g. new indication, new patient group) that will impact on prescribing costs to the commissioner. This includes where the prescribing will be passed on to primary care prescribers or where the drug is prescribed in hospital but generates additional PBR costs or is excluded from the Payment by Results Tariff and drug costs are passed on to commissioners. The annual horizon scanning process should be used as the preferred route to identify the majority of new developments, and any in-year funding applications will be subject to a prioritisation process to establish whether it is a local priority to review within the current financial year. Applicants are advised that prioritisation for review does not guarantee a positive commissioning recommendation outcome.

For minor formulary changes please use the Request for amendment to existing formulary choice or a medicine switch form.

This form is not to be used for Individual Funding Requests (IFR). These are considered where the individual or treatment is exceptional; i.e. where the treatment can be described as exceptional by virtue of the rarity of the condition or the difference of the individual from the generality of similar patients. Separate IFR documentation is available. Sometimes new, innovative treatment options are presented as exceptional: in this case every effort is made to direct the clinical team to the commissioning decision route, via this service development application, although the first few requests via the exceptional treatment route may be considered so as to offer benefit to patients where this is likely.

Process: Please complete this form as fully as possible. Please complete all relevant sections legibly and include full references. Any missing or illegible information will delay the application. You must discuss this application with the relevant Pharmacy Dept. / Medicines Management team within your organisation and obtain organisational support

and sign-off for the application before it is submitted. Applications completed by pharmaceutical companies are not acceptable.

Please submit completed form to your organisations representative on the Subgroup in your Pharmacy Dept / Medicines Management Team

Section 1 Clinical information	
Name of medicine (generic and brand name):	Brand name: Bijuve® Generic name: Estradiol 1mg / micronised progesterone 100mg ATC code is G03FA04 progesterone and estrogen. 06.04.01.01 Hormone replacement therapy Part VIIIA Category C Estradiol 1mg/progesterone 100mg was licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) for use in the United Kingdom in March 2021
Strength(s) and form(s) of preparation: Dose and schedule of administration:	Each pack contains 28 soft gelatin capsules containing 1 mg solubilised 17β-estradiol and 100mg micronised progesterone. 17β-estradiol is a body-identical hormone administered to replace depleted endogenous estrogen levels which decline naturally during the menopause. Progestogens are administered with estrogen replacement therapy to protect against endometrial hyperplasia and endometrial cancer in women with an intact uterus. Micronised progesterone and 17β-estradiol are both body identical hormones i.e., they are chemically and biologically identical to endogenous hormones. One capsule to be taken each evening with food.
Licensed indication(s):	Indicated for continuous combined hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women with intact uterus and with at least 12 months since last menses.
Proposed Indication (if different from or in addition to the above):	N/A

Section 1 Clinical information	
Is this treatment instead of or in addition to any current treatment? Please give details:	This treatment is in addition to currently available treatments. Bijuve® (estradiol 1mg/ mircronised progesterone 100mg) is the first approved oral continuous combined body-identical estradiol–progesterone formulation in a single capsule. Current HRT options for post-menopausal women with a uterus suffering from estrogen deficiency symptoms is either combined synthetic hormones or body-identical estrogen with concomitant synthetic progestogen, or free-dose combination body-identical estradiol and progesterone. There is currently no option for a regulated combined body-identical estradiol and micronised progesterone. It is important to note that the ratio of doses used in a combination of a separate estradiol and a separate oral progesterone (which are chosen by the prescriber) may not have been tested in a clinical trial. In addition, there is a potential for reduced compliance with free-dose combinations, which has been demonstrated in chronic conditions. Regulated bioidentical hormone replacement therapy (also known as body identical HRT) such as that offered by combined estradiol 1mg/progesterone 100mg, should not be confused with compounded bioidentical hormones which are unregulated and as such are not subject to the stringent efficacy, safety and quality requirements necessary to obtain regulatory approval from bodies such as the Medicines and Healthcare products Regulatory Agency (MHRA).

Section 1 Clinical information

Reason for proposed change. If replacing current treatment please state how it compares regarding efficacy and safety / tolerability	Bijuve® (estradiol 1mg/progesterone 100mg) is the first approved oral continuous combined body-identical estradiol–progesterone formulation in a single capsule. Real-world evidence suggests that use of regulated body-identical hormones are associated with lower risks compared to synthetic versions. With respect to the risk for breast cancer, heart disease, heart attack, and stroke, the evidence base demonstrates that body-identical hormones are safer forms of HRT. This is acknowledged in specific guidelines, for example the BMS consensus statement on bio-identical HRT. In terms of the use of micronised progesterone, in combination with body-identical estrogen, compared to synthetic versions of progesterone, real-world evidence suggests that there is: ▪ Significantly lower relative risk of breast cancer. ▫ The French E3N cohort study of >50,000 post-menopausal women showed that, compared to nonexposed women, the risk increased significantly for users of estrogens combined with progestogens (RR 1.3, 95% CI 1.1–1.5) but this increase was limited to synthetic progestins (RR 1.4, 95% CI 1.2–1.7); there was no evidence of increased risk associated with the use of estrogens combined with micronised progesterone (RR 0.9, 95% CI 0.7–1.2). The test for heterogeneity between micronised progesterone and synthetic progestins was significant ($p < 0.001$). ▪ A reduction in the increased risk of venous thromboembolism (VTE) conferred by oral estrogen.[i] The French ESTHER case–control study of post-menopausal women (271 cases of VTE and 610 controls) found that transdermal estradiol and micronised progesterone or pregnane derivatives (progestins derived from progesterone) were not associated with VTE risk compared to non-users (OR 0.7; 95% CI 0.3, 1.9 and 0.9; 95% CI 0.4, 2.3, respectively), whereas the use of non-pregnane derivatives increased VTE risk 4-fold compared to non-users (OR 3.9; 95% CI 1.5, 10.0). There is an unmet clinical need for HRT treatments that are convenient, well tolerated and offer an improved benefit risk profile compared to currently available treatments, with evidence suggesting that micronised progesterone, a body-identical hormone, may be better tolerated and associated with fewer risks than currently available synthetic progestogens.
Proposed place in therapy relative to other therapies (include protocol for use if available)	As an option for all eligible women Indicated for continuous combined hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women with intact uterus and with at least 12 months since last menses alongside other available treatments. Treatment will be considered based on patient preference and clinical judgement.

Section 1 Clinical information	
Predicted clinical impact on Primary Care e.g. will it be initiated in hospital only but then prescribed in primary care, or may it be initiated in primary care? Will it require shared care? Please describe:	Combined oral estradiol 1mg/progesterone 100mg is expected to be used in both primary and secondary care settings but is unlikely to meet local criteria for a shared-care agreement.
Monitoring requirements (e.g. for efficacy, side-effects) – if any? Do these differ from current situation?	Combined estradiol 1mg/progesterone 100mg is an oral preparation and does not require additional diagnostic testing or monitoring requirements over and above those for other HRT preparations available for the management of the indicated population. Due to anticipated improvements in critical quality of life measures such as reductions in the frequency and severity of moderate to severe VMS, or in sleep parameters, and endometrial safety benefits, an overall reduction in healthcare resource consumption may be expected.

Section 1 Clinical information

Brief summary of evidence in support of requested medicine / additional use. Meta-analyses, systematic reviews, double-blind randomised controlled trials in peer-reviewed journals. Ensure that evidence to support advantages / benefits of the new medicine over existing treatments is included where appropriate, including criteria for treatment success. Include any relevant morbidity, mortality, health economic and quality of life benefits.	REPLENISH was a phase III, 12-month, randomised, double-blind, placebo-controlled, multi-centre trial. Women (aged 40–65 years) with vasomotor symptoms and a uterus were randomised to daily oral estradiol (mg)/ progesterone (mg) (1/100, 0.5/100, 0.5/50, or 0.25/50). This represented the total population of 1835 women who received treatment. To investigate efficacy in managing VMS, some women (n=726) were entered into a vasomotor symptoms sub-study (women with moderate-to-severe hot flushes [seven or greater per day or 50 or greater per week]) to those estradiol–progesterone doses or placebo. The primary safety endpoint was endometrial hyperplasia incidence at 12 months (in the endometrial safety population), and the primary efficacy endpoints were mean changes in frequency and severity (from daily diaries) in moderate-to-severe vasomotor symptoms with estradiol– progesterone compared with placebo at weeks 4 and 12 in the vasomotor symptoms sub-study. Oral 1mg 17β-estradiol and 100mg micronised progesterone, demonstrated: • clinically relevant and statistically significant improvements in the frequency and severity of moderate-to-severe VMS were demonstrated for combined estradiol 1mg/progesterone 100mg compared to placebo at weeks 4 and 12 • clinically relevant and statistically significant improvements in MENQOL compared to placebo from baseline to week 12 and maintained up to 12 months • endometrial safety, with one case of simple endometrial hyperplasia without atypia reported, and no endometrial cancer at 12 months • > 90 % of amenorrhoea rate at cycle 13, with over 97% women experiencing absence of bleeding at cycle 13, demonstrating no difference in rates of no bleeding at cycle 13 between the treatment groups and placebo • a well-tolerated safety profile with no clinically significant differences in adverse events or risk factors for CVD and comparable rates of abnormal mammograms in the study group with 3.7% estradiol 1mg/progesterone 100mg, and 3.1% with placebo • no clinically meaningful impact on lipids, glucose, coagulation parameters, liver function tests, systolic or diastolic BP, or weight. Mean values for lipids and coagulation factors also remained within the normal limits. Up to three-quarters of post-menopausal women experience sleep disorders, which negatively impact health-related quality of life (HRQoL) and work productivity. Bijuve® demonstrated statistically significant improvements in sleep parameters compared to placebo from baseline to week 12 and sustained to month 12 in the REPLENISH clinical trial and is the only HRT with data to demonstrate meaningful improvement on sleep parameters in post-menopausal women.

Section 1 Clinical information

References
Please list and include copies or internet links with the application

- Theramex 2021, Summary of Product Characteristics
- Archer DF, Bernick BA, Mirkin S. A combined, bioidentical, oral, 17β-estradiol and progesterone capsule for the treatment of moderate to severe vasomotor symptoms due to menopause. Expert Rev Clin Pharmacol. 2019;12(8):729–39
- Kagan R, Constantine G, Kaunitz AM, Bernick B, Mirkin S. Improvement in sleep outcomes with a 17β-estradiol–progesterone oral capsule (TX-001HR) for postmenopausal women. Menopause. 2019;26(6):622–8.
- Lobo RA et al. Climacteric 2019; 22(6): 610-16.
- Liu JH et al. Menopause 2020; 27(12): 1388-95.
- Mirkin S et al. Menopause 2020; 27(4): 410-17.
- Mirkin S, Goldstein SR, Archer DF, Pickar JH, Graham S, Bernick B. Endometrial safety and bleeding profile of a 17β-estradiol/progesterone oral softgel capsule (TX-001HR). Menopause. 2020;27(4):410–7.
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- Simon JA, Kaunitz AM, Kroll R, Graham S, Bernick B, Mirkin S. Oral 17β-estradiol/progesterone (TX-001HR) and quality of life in postmenopausal women with vasomotor symptoms. Menopause. 2019;26(5):506–12.
- Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007;120(8):713–9.
- Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007;115(7):840–5.
- Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J cancer. 2005;114(3):448–54.
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- British Menopause Society. The British Menopause Society & Women's Health Concern 2016 recommendations on hormone replacement therapy in menopausal women. [Internet]. 2016. [Cited 27th August 2020]. Available from: https://thebms.org.uk/publications/consensus-statements/hormone-replacement-therapy/.
- National Institute for Health and Care Excellence. Menopause: diagnosis and management (NG23) [Internet]. 2015. [Cited 27th August 2020]. Available from: https://www.nice.org.uk/guidance/ng23/.
- National Institute for Health and Care Excellence. Menopause: diagnosis and management (NG23) Costing report/ template [Internet]. 2015. [Cited 22nd June 2021]. Available from: NICEhttps://www.nice.org.uk/guidance/ng23/resources

Section 2 Financial information

Costs: (excluding VAT)
Cost per patient per year of medicine:

Combined estradiol 1mg/progesterone 100mg will be available at a cost of £8.14 per 28-day pack.

Combined estradiol 1mg/progesterone 100mg is available at the same price as the widely used Femoston® Conti, and it has the potential to deliver cost savings versus most available alternatives, given the potential cost savings related to the unnecessary management of poor symptomatic control, inappropriately prescribed sleeping or anti-depressant medication, or management of complications arising from the current use of synthetic HRT, or free dose options.

Number of patients per year to be treated for the whole organisation: *Where possible / applicable, include assessment of patient numbers across [redacted] area.*

The following estimate of population size eligible for combined estradiol 1mg/progesterone 100mg is based largely on the most recent NICE National Costing Report, and assumes menopausal women over 50, without a hysterectomy, and eligible for continuous combined oral HRT are candidates for treatment.

Estimated eligible patients / uptake per 100,000 population			
Per 100,000 population	100,000		
⇒ Prevalence of women aged 50+ with menopausal symptoms[42]	2,906		
⇒ Number of non-hysterectomised patients (80%)[43,44]	2,325		
⇒ Proportion using oral HRT (55%)*	1,279		
⇒ Proportion using continuous combined HRT (50%)†	639		
⇒ Anticipated uptake (share of oral continuous combined HRT) §	Year 1 (5%)	Year 2 (15%)	Year 3 (20%)
⇒ **Treated women**	**32**	**96**	**128**

Additional costs e.g. day case tariff, tests per patient per year:

Any impact on PBR activity? Please give details:

*Theramex estimate based on commercial insight
†Theramex estimate based on commercial insight
§Theramex estimate

Overall financial impact:

Neutral

Section 2 Financial information

Current treatment(s) usually used (if any):

Cost per patient per year currently treated (excluding VAT):

	Pack size	Form	NHS pack price	NHS price per 28 days
Elleste Duet Conti	84	tablet	£17.02	£5.67
Femoston Conti	84	tablet	£24.43	£8.14
Indivina	84	tablet	£20.58	£6.86
Kliofem	84	tablet	£11.43	£3.81
Kliovance	84	tablet	£ 13.20	£4.40
Premique Low Dose	84	tablet	£6.52	£2.17
Average 28 day price (assuming equal weighting)				*£5.18*

Number of patients per year currently treated:

Current additional costs e.g. day case tariff, tests per patient per year:

Using combined estradiol 1mg/progesterone 100mg instead of older or synthetic HRT options, may incur slight increases to the drug budget, but is likely to drive larger savings in the costs associated with avoidance of unnecessary health care consumption required to manage poorly controlled patients or the safety issues associated with older products.

Per 100,000 population, we expect up to 128 patients to be eligible for combined estradiol 1mg/progesterone 100mg, after three years of availability. Allowing all of these patients to access combined estradiol 1mg/progesterone 100mg, and assuming that older products are available at an unweighted average price, the increase in drug budget would be just under £5,000 per year across the whole population.

Section 2 Financial information	
Predicted financial impact on Primary Care. e.g. Is the medicine hospital only but PBR excluded, will it be initiated in hospital only but then prescribed in primary care, or may it be initiated in primary care? Please describe:	As above. Combined oral estradiol 1mg/progesterone 100mg is expected to be used in both primary and secondary care settings.
Section 3 Conflicts of Interest	
Please state any potential conflicts of interest e.g. funding of research, equipment, consulting or speaking fees, other personal or non-personal or family interest etc. in relation to this request:	

Name of Applicant

Role

Organisation name:

I confirm I have sent a copy of this form to my organisations Drug & Therapeutics Committee / Medicines Management Committee or equivalent, and it has been approved following the appropriate procedure within my organisation.

Signature of Applicant

Name of Clinical Director / CCG Prescribing Lead

Preparation date: November 2021

Job Code: Bijuva_GB_FORKIT_005984

Signature Clinical Director / Prescribing Lead

Name of Chief Pharmacist / Head of Medicines Management

Signature of Chief Pharmacist / Head of Medicines Management

Please note that the application will not be considered unless the Chief Pharmacist / Clinical Director / Prescribing Lead / Head of Medicines Management in your organisation has signed this form.

[i] Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007;115(7):840–5.

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