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Prescribing hormone replacement therapy (HRT) in postmenopausal women: a focus on Oestrogel® (estradiol) and Utrogestan® 100 mg (micronised progesterone)

Reviewed and co-authored by: Michael Savvas, Consultant Gynaecologist, King's College Hospital

Prescribing and adverse events reporting information can be found on pages 6–7.

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Indications

Oestrogel (estradiol) is indicated for:

1. Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women
2. Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

The experience treating women older than 65 years is limited.

Utrogestan 100 mg (micronised progesterone) is indicated for adjunctive use with oestrogen in postmenopausal women with an intact uterus as HRT.

If you have any questions on either of these products, please contact

information@besins-healthcare.com

or visit:

www.oestrogel.co.uk

www.utrogestan.co.uk

Foreword: Hormone replacement therapy

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Hormone replacement therapy (HRT) is effective in alleviating the various climacteric symptoms, which include hot flushes, poor sleep, tiredness, mood swings, headaches, and loss of libido.[1–3] In the long term HRT can also prevent osteoporosis, reduce the risk of osteoporotic fractures, and reduce the risk of heart disease.[2,3]

Anxiety remains regarding the risk of breast cancer, which deters many women from taking HRT.[2] However, the current evidence is reassuring. The NICE guidelines on menopause state that:[2]

- HRT with oestrogen alone is associated with little or no change in the risk of breast cancer
- HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer
- any increase in the risk of breast cancer is related to treatment duration and reduces after stopping HRT.

The increased risk of breast cancer with combined oestrogen and progestogen HRT is small and is less than the risk of breast cancer seen with some avoidable risk factors, such as being overweight or obese.[3] The type of progestogen used in combined HRT appears to be important and there is evidence that combined HRT with micronised progesterone for up to 5 years does not increase the risk of breast cancer as seen with synthetic progestogens such as medroxyprogesterone acetate.[4,5]

There is no evidence that HRT results in an increased mortality from breast cancer. A long-term follow-up study of two randomised trials found that conjugated equine oestrogen (CEE) alone was significantly associated with a lower breast cancer incidence and breast cancer mortality versus placebo.[6] CEE plus medroxyprogesterone acetate was significantly associated with a higher breast cancer incidence but no significant difference in breast cancer mortality versus placebo.[6]

Some women are progestogen intolerant, experiencing side effects such as mood changes, headaches, and tiredness, which can limit the use of HRT.[7] These side effects are largely seen with the synthetic progestogens; they can be avoided with micronised progesterone.[7]

More than a quarter (27%) of all deaths in the UK are caused by cardiovascular disease.[8] Both combined and unopposed oestrogen replacement have been reported to reduce the incidence and mortality from cardiovascular disease if started before the age of 60 years.[3]

There is an increased risk of venous thromboembolism (VTE) when taking oral HRT (combined or unopposed).[9,10] In women using transdermal oestrogen alone, there was no increase in the risk of VTE.[9,10] For transdermal HRT combined with a progestogen, the risk of VTE depends upon which progestogen is used; there is no change in VTE risk in women using micronised progesterone.[9] Transdermal rather than oral HRT can be prescribed in women who at increased risk of VTE.[2]

HRT is an effective treatment for menopausal symptoms resulting in improved quality of life. In the long term, the benefits of HRT far outweigh any theoretical risks and the all-cause mortality is reduced in women taking HRT.[3] HRT can be prescribed as long as the woman requires it with no arbitrary time limits.[3,11]

Conflicts of interest

Michael Savvas declared no conflicts of interest.

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Prescribing hormone replacement therapy (HRT) in postmenopausal women: a focus on Oestrogel® (estradiol) and Utrogestan® 100 mg (micronised progesterone)

Reviewed and co-authored by: Michael Savvas, Consultant Gynaecologist, King's College Hospital

Individualised approach to HRT

NICE recommends that prescribers adopt an individualised approach to prescribing HRT through emphasising individual preferences based on an overall balance of indication, short- and long-term benefits, and risks (Box 1).[1]

Box 1: Taking an individualised approach

Menopause and its treatment

- Explain stages of menopause
- Identify short-term symptoms
- Discuss and consider lifestyle changes
- Discuss benefits and risks of treatments
- Discuss long-term implications of menopause.

Oestrogel and Utrogestan 100 mg

Oestrogel is a body identical oestrogen transdermal gel that is indicated for oestrogen deficiency symptoms in postmenopausal women.[2,3]

Utrogestan 100 mg is an oral capsule of body identical micronised progesterone and is indicated for adjunctive use with oestrogen in postmenopausal women with an intact uterus, as HRT.[3,4]

Efficacy

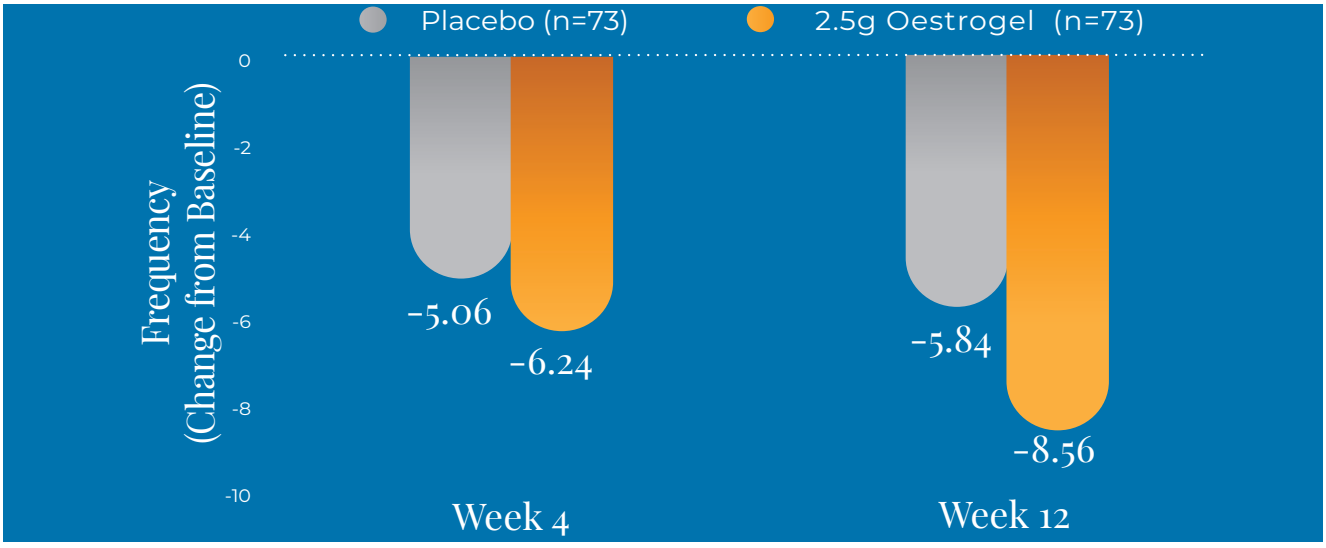
Vasomotor symptoms

NICE recommends that women should be offered HRT for vasomotor symptoms after discussing with them the short-term and longer-term benefits and risks. Women without a uterus should be offered oestrogen alone. Women with a uterus should be offered oestrogen and progestogen.[1]

A double-blind, randomised, placebo-controlled study (n=221) showed that Oestrogel significantly reduced the frequency of moderate-to-severe hot flushes at week 12 compared with placebo (82% versus 57% mean reduction, $p<0.001$, Figure 1) on the starting dose.[5,6] Oestrogel was shown to be as effective as oral oestrogen and transdermal oestrogen patches at relieving vasomotor symptoms.[7–9]

Combining oestrogen with micronised progesterone in women with an intact uterus protected the endometrium from hyperplastic changes associated with oestrogen-only therapy.[10] Micronised progesterone plus oestrogen also reduces the number of bleeding days versus medroxyprogesterone acetate plus oestrogen by 23% (over 3 years; $p\leq0.01$).[11]

Figure 1: Reductions in frequency of moderate-to-severe hot flushes



Adapted from Archer D, *et al. Menopause*. 2012;19(6):622–629.

Breast cancer

The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestogen or oestrogen-only HRT that is dependent on the duration of taking HRT. 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 is taken for more than 5 years, the risk may persist for 10 years or more.[12] Oestrogel and Utrogestan are contraindicated in known, past or suspected breast cancer.[2,4]

Venous thromboembolism

HRT is associated with an increased risk of venous thromboembolism (VTE), however transdermal oestrogen does not significantly increase that risk in users when compared to non-users.[2,13–18] NICE recommends transdermal rather than oral HRT for menopausal women who are at increased risk of VTE.[1] Unlike other progestogens, there is no significant association of VTE with micronised progesterone.[4,14,16,19] Oestrogel and Utrogestan are contraindicated in previous or current VTE disorders.[2,4]

Warnings and precautions

Please refer to the Oestrogel and Utrogestan 100 mg Summaries of Product Characteristics for the full list of warnings, precautions, contraindications, and adverse events.[2,4]

Utrogestan 100 mg contains soya lecithin. As there is a possible relationship between allergy to soya and allergy to peanut, people with soya or peanut allergy should avoid using this medicine.[4] For the avoidance of doubt, Utrogestan 100 mg does not contain peanut products.

How to start a patient on Oestrogel and Utrogestan 100 mg

Oestrogel[2]

For women who have never taken HRT and are postmenopausal or have very infrequent menstrual cycles, treatment with Oestrogel can be started on any day. For women switching from a continuous oestrogen-progestogen combined HRT, treatment with Oestrogel can be started on any day of the cycle. For women switching from a cyclic or continuous sequential HRT treatment, the patient should finish the therapeutic sequence before beginning treatment with Oestrogel.

Utrogestan 100 mg[4]

In postmenopausal women with an intact uterus, two regimens of Utrogestan 100 mg are possible based on the bleeding pattern desired:

- 100 mg daily at bedtime from day 1 to day 25 of the cycle; withdrawal bleeding is less with this schedule
- 200 mg daily at bedtime for 12 days starting on day 15 of the cycle ending on day 26; withdrawal bleeding may occur in the following week.

Conclusion

When following menopausal guidelines Oestrogel and Utrogestan 100 mg are body identical options for the management of postmenopausal symptoms in women with an intact uterus.[2–4] Separate micronised progesterone allows dose tailoring of the oestrogen component to provide an individualised approach.[4]

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Prescribing Information

Oestrogel (estradiol) Pump-Pack

For full prescribing information, including side effects, precautions and contraindications, please consult the Summary of Product Characteristics (SPC).

Presentation: Transdermal gel containing 17β-estradiol 0.06% w/w. Each pump actuation is 1.25 g of Oestrogel, which contains 0.75mg of 17β-estradiol. **Indication:** 1: Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women. 2: Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. The experience treating women older than 65 years is limited. **Dosage and Administration:** Oestrogel is an oestrogen-only product to be administered daily on a continuous basis for women without a uterus. In women with an intact uterus, a progestogen should be added for at least 12 days each month. The pump pack will require priming before using a new pump pack for the first time. The first dose dispensed should be discarded. The gel should be applied to at least 750 cm^2 of clean, dry, intact areas of skin (e.g. arms, shoulders, inner thighs). It should not be applied on or near the breasts or on the vulval region. The patient should apply the gel herself and avoid skin contact with others, particularly a male partner, for at least 1 hour after application. *Menopausal and postmenopausal symptoms:* The usual starting dose is 2 pumps (2.5 g containing 1.5 mg 17β-estradiol) once daily. If effective relief is not obtained after one month's treatment, this may be increased to a maximum of 4 measures (5 g containing 3.0 mg estradiol) daily. For initiation and continuation of treatment, the lowest effective dose for the shortest duration should be used. *Prevention of postmenopausal osteoporosis:* The minimum effective dose is 2.5 g Oestrogel once daily. For full details of usage please refer to the SPC. **Contraindications:** Hypersensitivity to estradiol or any of the excipients; 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, active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction); acute liver disease or history of liver disease whilst liver function tests are abnormal; porphyria. **Warnings and Precautions:** HRT should only be initiated for symptoms that adversely affect quality of life. The risks and benefits should be reviewed annually and HRT only continued as long as the benefit outweighs the risk. A personal and family medical history should be taken before initiating or reinstituting HRT. Periodic check-ups are recommended during treatment. Physical examination and investigations including appropriate imaging tools should be carried out according to the clinical needs of the patient. Patients should be closely supervised if any of the following conditions are present, have occurred previously and/or have been aggravated during pregnancy or previous hormone treatment since they may recur or be aggravated during treatment with Oestrogel: leiomyoma (uterine fibroids) or endometriosis; risk factors for thromboembolic disorders; risk factors for oestrogen-dependent tumours; hypertension; liver disorders; diabetes mellitus with or without vascular involvement; cholelithiasis; migraine or severe headache; systemic lupus erythematosus; history of endometrial hyperplasia; epilepsy; asthma and otosclerosis. Oestrogel should be discontinued if a contraindication is discovered or the following occur: jaundice or deterioration in liver function; significant increase in blood pressure; new onset of migraine-type headache; pregnancy. In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered for prolonged periods of time. Break through bleeding and spotting may occur during the first months of treatment but if they occur after some time on therapy or continue after treatment has been discontinued the reason should be investigated. Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestogen or oestrogen-only HRT that is dependent on the duration of taking HRT. HRT increases the density of mammographic images which may adversely affect the radiological detection of breast cancer. Evidence suggests a slight increased risk of ovarian cancer in women taking oestrogen-only or combined oestrogen-progestogen HRT. HRT is associated with a 1.3 to 3-fold risk of developing venous thromboembolism (i.e. deep vein thrombosis or pulmonary embolism) especially in the first year of use. HRT should be stopped 4 to 6 weeks prior to elective surgery if prolonged immobilisation is to follow. The benefit-risk of HRT should be considered in women already on chronic anticoagulant treatment. If venous thromboembolism occurs during treatment, HRT should be discontinued. Patients should contact their doctors immediately if they have potential thromboembolic symptoms (painful swelling of a leg, sudden chest pain or dyspnoea). Combined oestrogen-progestogen and oestrogen-only therapy are associated with up to a 1.5-fold increase in risk of ischaemic stroke. The risk increases with age. Care should be taken with women with cardiac or renal dysfunction since oestrogens may cause fluid retention. Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or HRT since pancreatitis can result from rare cases of large increases in plasma triglycerides. Oestrogens increase binding proteins such as thyroid, corticoid and sex-hormone binding globulins leading to increased circulating hormones. There is some evidence of increased risk of probable dementia in women who start HRT after the age of 65. **Interactions:** Patients should avoid strong skin cleaners and detergents, skin products of high alcoholic content (e.g. astringents, sunscreens) and keratolytics which may alter the barrier structure or function of the skin. Also, any skin medication which alters skin production (e.g. cytotoxic drugs) should be avoided. The metabolism of oestrogens may be increased, (leading to a decreased effect and changes in the uterine bleeding profile) by enzyme-inducing products (e.g. phenobarbital, phenytoin, carbamazepine, rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir, nelfinavir and St John's wort may also induce the metabolism of oestrogens. As transdermal administration avoids the first pass effect in the liver, transdermally applied oestrogens may be less affected by enzyme inducers than oral hormones. **Pregnancy and breastfeeding:** Oestrogel is not indicated in pregnancy or during breastfeeding. If pregnancy occurs during medication with Oestrogel, the treatment should be withdrawn immediately. **Undesirable effects:** The following commonly (≥1/100; ≤1/10) occur with HRT: headache, nausea, abdominal pain, breast swelling/pain, breast enlargement, dysmenorrhoea, menorrhagia, metrorrhagia, leucorrhoea, endometrial hyperplasia, weight change (increase or decrease), water retention with peripheral oedema. The following uncommonly (≥1/1,000; <1/100) occur with HRT: depression, mood swings, vertigo, migraine, venous thromboembolic disease, flatulence, vomiting, pruritus, benign breast neoplasm, increased volume of uterine, leiomyoma, vaginitis/vaginal candidiasis, asthenia. The following risks apply in relation to systemic oestrogen/progestogen treatment: breast cancer; endometrial cancer; ovarian cancer; venous thromboembolism; coronary artery disease; ischaemic stroke. For further information on side effects and risk estimates, please consult the SPC. **Overdose:** Symptoms may include breast pain, excessive production of cervical mucous, nausea, and withdrawal bleeding. There are no specific antidotes and treatment should be symptomatic.

NHS Price: 80g dispenser £4.80. **Legal category:** POM. **Marketing Authorisation number:** PL 28397/0002. **Marketing Authorisation Holder:** Besins Healthcare, Avenue Louise, 287, Brussels, Belgium. **Date of preparation of Prescribing Information:** September 2021 OES/2021/033

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Besins Healthcare (UK) Ltd, Drug Safety on 0203 862 0920 Email: pharmacovigilance@besins-healthcare.com

Prescribing Information UTROGESTAN (progesterone) 100 mg CAPSULES

For full prescribing information, including side effects, precautions and contraindications, please consult the Summary of Product Characteristics (SPC).

Presentation: Soft white capsule containing 100 mg micronised progesterone. **Indication:** Adjunctive use with oestrogen in post-menopausal women with an intact uterus as HRT. **Dosage and Administration:** Oral capsules which should not be taken with food as this increases the bioavailability of the capsules. The recommended dose is 2 capsules daily at bedtime for twelve days in the last half of each therapeutic cycle (Day 15 to 26). Withdrawal bleeding may occur in the following week. Alternatively, 1 capsule can be given at bedtime from Day 1 to Day 25 of each therapeutic cycle, withdrawal bleeding being less with this treatment schedule. Dose for elderly is the same. Not indicated in children. For full details of usage see SPC. **Contraindications:** Known past or suspected breast cancer; hypersensitivity to progesterone, soybean lecithin, peanut or any of the excipients; undiagnosed genital bleeding; known or suspected estrogen-dependent malignant tumours (e.g. genital tract carcinoma); thrombophlebitis; thrombophilic disorders; acute liver disease or history of liver disease; previous or current thromboembolism disorders; cerebral haemorrhage; porphyria, breast-feeding. **Warnings and Precautions:** HRT should only be initiated for symptoms that adversely affect quality of life. 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. Women should be encouraged to be aware of their breasts and report any changes to their doctor or nurse. 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. Utrogestan 100mg is not a treatment for premature labour, in confirmed pregnancy or as a contraceptive. Conditions which may need supervision: The following may recur or be aggravated during treatment with Utrogestan 100 mg: leiomyoma or endometriosis; risk factors for thromboembolic disorders, risk factors for oestrogen dependent tumours (e.g. 1st degree heredity for breast cancer), hypertension, liver disorders (e.g. liver adenoma); diabetes mellitus; cholelithiasis; migraine or severe headache; systemic lupus erythematosus; endometrial hyperplasia; epilepsy; asthma; otosclerosis; depression; photosensitivity. Therapy should be immediately discontinued if the following occur: jaundice or deterioration in liver function, significant increase in blood pressure, new onset of migraine, pregnancy, unexplained loss of vision, proptosis or diplopia, papilloedema, retinal vascular lesions. The use of HRT is associated with an increased risk of deep vein thrombosis (DVT) or pulmonary embolism. The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT. Combined oestrogen-progestagen are associated with an increased risk of ischaemic stroke. Utrogestan 100 mg Capsules contain soybean lecithin and may cause hypersensitivity reactions (urticarial and anaphylactic shock in hypersensitive patients). As there is a possible relationship between allergy to soya and allergy to peanut, patients with peanut allergy should avoid using Utrogestan 100mg Capsules. FOR THE FULL LIST OF WARNINGS AND PRECAUTIONS PLEASE CONSULT SECTION 4.4 OF THE FULL SPC. **Interactions:** Drugs known to induce the hepatic CYP450-3A4 (e.g. barbiturates, anti-epileptic agents (phenytoin, carbamazepine), rifampicin, phenylbutazone, bromocriptine, spironolactone, griseofulvin, some antibiotics (ampicillins, tetracyclines) and herbal products containing St. John's wort, may increase metabolism and the elimination of progesterone. Ketokonazole and other inhibitors of CYP450-3A4 such as ritonavir and nelfinavir may increase bioavailability of progesterone. Utrogestan 100mg may raise the plasma concentration of ciclosporin, diazepam, tizanidine. Aminoglytethimide reduces plasma concentrations of medroxyprogesterone acetate and megestrol. Progesterone may enhance or reduce the anticoagulant effect of coumarins. Progesterone antagonises the anticoagulant effect of phenindione. Use of ulipristal acetate reduces efficacy of progesterone. An adjustment in anti-diabetic dosage may be required. Breakthrough bleeding may occur when using terbinafine with Utrogestan 100mg. They may also affect the laboratory tests of hepatic and/or endocrine functions. **Pregnancy and lactation:** If pregnancy occurs during medication, Utrogestan 100mg should be withdrawn immediately. Prescription of progesterone beyond the first trimester may reveal gravidic cholestasis. Utrogestan 100mg is not indicated during breast-feeding. Progesterone is distributed into breast milk. **Effects on ability to drive and use machines:** Utrogestan 100mg may cause drowsiness and/or dizziness. **Undesirable effects:** *Frequency not known, from post-marketing experience:* Abdominal pain, nausea, fatigue, headache, somnolence, dizziness, vaginal haemorrhage, pruritus. The following risks apply in relation to systemic oestrogen/progestogen treatment: breast cancer; endometrial cancer; ovarian cancer; venous thromboembolism; coronary artery disease; ischaemic stroke. For further information on side effects and risk estimates please consult the SPC of both products. **Overdose:** Symptoms may include drowsiness, somnolence, dizziness, or fatigue. **NHS Price:** Utrogestan 100 mg capsules - £5.13 for 30 capsules. **Legal category:** POM. **Marketing Authorisation Number:** Utrogestan 100 mg capsules - PL 28397/0003. **Marketing Authorisation Holder:** Besins Healthcare, Avenue Louise, 287, Brussels, Belgium. **Date of preparation of prescribing information:** October 2020 BHUK/2020/098

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