

**micronised progesterone, 100mg, 200mg capsules (Utrogestan®)
No. (542/09)**

Ferring Pharmaceuticals Ltd

06 March 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

micronised progesterone (Utrogestan®) is not recommended for use within NHS Scotland for adjunctive use with oestrogen in post-menopausal women with an intact uterus (HRT).

Micronised progesterone was as effective as another progestogen in protecting the endometrium from the hyperplastic changes associated with oestrogen therapy.

However, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Adjunctive use with oestrogen in post-menopausal women with an intact uterus (HRT)

Dosing information

The recommended dose is 200mg daily at bedtime, for twelve days in the last half of each therapeutic cycle (beginning on day 15 of the cycle and ending on day 26). Withdrawal bleeding may occur in the following week. Alternatively 100mg can be given at bedtime from day 1 to day 25 of each therapeutic cycle, withdrawal bleeding being less with this treatment schedule.

Product availability date

June 2007

Summary of evidence on comparative efficacy

The addition of a progestogen (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer in post-menopausal women receiving oestrogen replacement therapy. Micronised progesterone has all the properties of endogenous progesterone, the main hormone of the corpus luteum and the placenta. It has gestagenic, anti-oestrogenic, slightly anti-androgenic and anti-aldosterone effects and acts on the endometrium by converting the proliferating phase to the secretory phase.

The submitting company has suggested that micronised progesterone is likely to be reserved for patients intolerant of synthetic progestogens or for those with diabetes or a family history of breast cancer.

The evidence is from a 3-year, multicentre trial that compared the efficacy of micronised progesterone with placebo and with two different medroxyprogesterone acetate (MPA) treatment regimens. It investigated the following outcomes:

- coronary risk, (the primary objective) (lipid metabolism, blood pressure, carbohydrate metabolism, and coagulation/haemostasis)
- endometrial safety
- bleeding patterns

Patients with or without a uterus were included if they had: cessation of menses between 1 and 10 years prior to enrolment, or were surgically menopausal with a follicle-stimulating hormone level of at least 40IU/L, and a normal or atrophic endometrial biopsy result and normal mammogram at baseline. A total of 875 postmenopausal women between 45 and 64 years participated. Only 596 of these had an intact uterus. (This trial was carried out prior to 1995 and the absence of a uterus did not affect treatment randomisation).

The women were randomised to one of the following treatments in a 28-day cycle: placebo; 0.625 mg/day conjugated equine oestrogens (CEE); 0.625mg/day CEE plus 2.5mg/day MPA; 0.625mg/day CEE plus 10mg/day MPA for the first 12 days; or 0.625mg/day CEE plus 200mg/day micronised progesterone for the first 12 days.

An analysis of the 596 women with intact uterus revealed endometrial hyperplasia rates after three years of 2.5%, 62%, 1%, 5% and 5% for the placebo, oestrogen monotherapy, oestrogen plus continuous MPA, oestrogen plus cyclic MPA, and oestrogen plus micronised progesterone groups, respectively.

Analysis of episodes of excess bleeding in women with a uterus who took at least 80% of their assigned medication demonstrated that the 3-year cumulative quantities, days, and episodes of bleeding were significantly lower for oestrogen plus cyclic micronised progesterone than for oestrogen plus cyclic MPA.

Intention-to-treat analyses found mean changes from baseline in high-density lipoprotein cholesterol (HDL-C) of: placebo (decrease of 0.03mmol/L); MPA regimens (increases of 0.03 to 0.04mmol/L); oestrogen plus micronised progesterone (increase of 0.11mmol/L) and oestrogen monotherapy (increase of 0.14mmol/L). For all hormone regimens, HDL-C levels increased during the first 6 to 12 months and gradually decreased thereafter, although not to baseline level. Women treated with oestrogen plus micronised progesterone had significantly higher HDL-C levels than women treated with oestrogen plus MPA. All active treatments produced decreases in mean low-density lipoprotein cholesterol (of 0.37 to 0.46mmol/L), and increases in mean triglyceride (of 0.13 to 0.15mmol/L) that differed significantly from placebo.

Placebo was associated with a significantly greater increase in mean fibrinogen than any active treatment (0.10g/L compared with -0.02 to 0.06g/L); differences among active treatments were not significant. Systolic blood pressure increased and post-challenge insulin levels decreased during the trial, but neither varied significantly by treatment assignment.

Summary of evidence on comparative safety

In the pivotal trial described above, there was no difference in adverse effects between the micronised progesterone and medroxyprogesterone treatment arms.

A prospective French cohort trial assessed the association between different HRT regimens and breast cancer risk. During follow-up, (mean duration 8.1 postmenopausal years), 2,354 cases of invasive breast cancer occurred among 80,377 postmenopausal women. The association of oestrogen–progestogen combinations with breast cancer risk varied significantly according to the type of progestogen: compared with never-users, the relative risk was 1.00 (95% CI: 0.83 to 1.22) for oestrogen plus a natural micronised progesterone, 1.16 (95% CI: 0.94 to 1.43) for oestrogen plus dydrogesterone and 1.69 (95% CI: 1.50 to 1.91) for oestrogen combined with other progestogens.

Summary of clinical effectiveness issues

There are two main types of progestogen: progesterone and its (C21) analogues (dydrogesterone and MPA) and testosterone (C19) analogues, (norethisterone, norgestrel, desogestrel, norgestimate, gestodene and levonorgestrel). The progesterone analogues are less androgenic and neither progesterone nor dydrogesterone causes virilisation.

Micronised progesterone is the only available oral formulation of progesterone. The pivotal trial demonstrated that micronised progesterone at a dose of 200mg daily for 12 days of the cycle was as effective as the two MPA regimens in protecting the endometrium from the hyperplastic changes associated with oestrogen therapy.

No evidence on the use of the 100mg dose of micronised progesterone was submitted. Micronised progesterone compared favourably with MPA with respect to bleeding patterns and lipid metabolism. Limited safety evidence suggests a lower risk of breast cancer with

micronised progesterone compared with synthetic progestogens. There is no trial evidence comparing micronised progesterone with its closest analogue, dydrogesterone. Neither is there evidence comparing micronised progesterone with synthetic progestogens administered by non-oral routes, eg. levonorgestrel intrauterine system which SMC experts have indicated is an option for patients intolerant of oral synthetic progestogens.

Most HRT treatments are provided in fixed-dose combination packs. Currently there are limited prescribing options if patients are intolerant of the adverse effects of synthetic progestogens. A recent systematic review suggested a lower risk of venous thromboembolism with transdermal compared with oral oestrogen. However, there is little choice of a concomitant non-androgenic progestogen if oestrogen is to be administered by the transdermal route.

The submitting company has suggested that micronised progesterone is likely to be used in patients intolerant of the adverse effects, (especially androgenic effects) of synthetic progestogens, or for those with diabetes or a family history of breast cancer, however there is no evidence of efficacy in these specific patient populations.

Summary of comparative health economic evidence

The manufacturer submitted a simple drug budget impact analysis comparing micronised progesterone with MPA in post-menopausal women with an intact uterus. The pivotal clinical trial showed that micronised progesterone was as effective as two different MPA regimens with respect to protecting the endometrium against oestrogen induced hyperplasia. The manufacturer estimated that the introduction of micronised progesterone would result in an increased cost of £15.48 per patient per year.

The main weaknesses of the analysis were:

- No formal economic evaluation was carried out; only a very simple drug cost comparison was presented showing the increased cost of micronised progesterone treatment compared with MPA.
- The comparator used was inappropriate given the positioning of micronised progesterone as a second-line therapy for patients unable to tolerate synthetic progestogens. The manufacturer compared the drug costs of micronised progesterone with MPA. However, SMC clinical expert replies indicated that levonorgestrel intra-uterine system (IUS) may be used in patients who are intolerant of synthetic progestogens. No clinical evidence or drug cost comparison was presented comparing micronised progesterone with levonorgestrel IUS) or with existing oestrogen/anti-androgenic progestogen combinations.

Due to the lack of formal economic analysis to justify the additional cost of the treatment and the inappropriate comparator the manufacturer has not presented a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

Micronised progesterone is the only oral progestogen available that is equivalent to endogenous progesterone. Analogues are dydrogesterone, (available only in combination with oestrogens), and medroxyprogesterone acetate (MPA), (available alone and in combination with oestrogens). Testosterone analogue progestogens used in HRT include norethisterone, norgestrel, desogestrel, norgestimate, gestodene and levonorgestrel. An intrauterine system containing levonorgestrel releases low dose drug directly into the uterine cavity, thereby minimising systemic effects.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
<u>Progestogen alone</u>		
micronised progesterone	200mg daily for 12 days of cycle or 100mg daily for 25 days of cycle	59 or 62
medroxyprogesterone acetate	10mg orally daily for 12 days of cycle	36
levonorgestrel	intrauterine system 52mg over four years	21

Combined oestrogen/progestogen

estradiol patch plus micronised progesterone 200mg tablets	one (40micrograms/24 hours) estradiol patch transdermally twice weekly plus 200mg micronised progesterone orally daily for 12 days of cycle	124
estradiol patch plus dydrogesterone tablets	one (40micrograms/24 hours) estradiol patch transdermally twice weekly plus 10mg dydrogesterone orally daily for 14 days of cycle	99
estradiol tablets plus micronised progesterone tablets	2mg estradiol orally daily plus 200mg micronised progesterone orally daily for 12 days of cycle	81
estradiol tablets plus dydrogesterone tablets	2mg estradiol orally daily for 14 days of cycle plus 2mg estradiol combined with 10mg dydrogesterone orally daily for remaining 14 days of cycle	58

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 05 January 2009.

Additional information: budget impact

The manufacturer estimated a net drug budget impact of £15,505 per annum based on current prescriptions for combined HRT in Scotland. The manufacturer estimated 942 patients would be eligible for micronised progesterone based on an assumption that 10% of women experience side effects with synthetic progestogen. Patient numbers were assumed to be stable each year on the basis that the number of patients discontinuing treatment would roughly balance out the number of new patients. The figures do not allow for use of any alternative options e.g. levonorgestrel IUS and the net impact assumes micronised progesterone would displace single agent MPA. The manufacturer's estimate of the number of patients on HRT in Scotland may be an underestimate.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 13 February 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

The Writing Group for the PEPI Trial. Effects of estrogen or estrogen-progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen-Progestin Interventions (PEPI) Trial. JAMA 1995; 273(3): 199-208.

The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen-Progestin Interventions (PEPI) Trial. JAMA 1996; 275(5): 370-375.

Barrett-Connor E, Slone S, Greendale G, et al. The Postmenopausal Estrogen-Progestin Interventions Study: primary outcomes in adherent women. Maturitas 1997; 27(3): 261-274.

Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat 2008; 107(1): 103-111.

Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. Canonico M, Plu-Bureau G, Lowe GD et al BMJ. 2008, 336(7655):1227-31