Hertfordshire and West Essex Integrated Care System

NHS Hertfordshire and West Essex Integrated Care Board

Oral micronised progesterone (Utrogestan®) for adjunctive use with oestrogen in menopausal women with an intact uterus as Hormone Replacement Therapy (HRT)

GREEN – RECOMMENDED FOR USE IN PRIMARY AND SECONDARY CARE

Name: generic (trade)	What it is	Indication	Date decision last revised	Decision status	NICE / SMC Guidance
Oral micronised progesterone (Utrogestan®)	Hormone Replacement Therapy	Adjunctive use with oestrogen in post-menopausal women with an intact uterus, as HRT	March 2022	Final	• NICE – women with an intact uterus should be prescribed oestrogen and progestogen • SMC – not recommended

Recommendation:

Green across Hertfordshire and west Essex (i.e. suitable for primary care and secondary care prescribing) within licensed indications as an option for adjunctive use with oestrogen in menopausal women with an intact uterus as HRT.

Background Information:

- As women near the menopause, the production of female hormones oestrogen and progesterone decreases in the body. An oestrogen deficiency in the menopause is associated with irregular periods, and eventual amenorrhoea. Vasomotor symptoms are common and include: hot flushes, night sweats, vaginal atrophy, mood changes, sexual dysfunction (including loss of libido), memory and concentration changes, headaches, joint and muscle complaints.
- Oestrogen alone is suitable for woment without a uterus. The addition of progesterone is required for women with an intact uterus to prevent cystic hyperplasia of the endometrium and possible transformation to cancer, which can occur with unopposed oestrogen exposure.[1]
- The progestogens used for HRT are synthetic versions of the hormone progesterone (such as dydrogesterone, medroxyprogesterone, norethisterone and levonorgestrel), or micronised progesterone (sometimes called body identical, or natural), which is chemically identical to the human hormone.[2]
- Of the synthetic progestogens listed above, dydrogesterone is only available in combination with estradiol (an oestrogen). Medroxyprogesterone is indicated for progestogenic opposition of oestrogen HRT, however the brand Provera® in all available strengths is unlicensed for use in HRT.[3] Climanor® (medroxyprogesterone 5 mg) is currently unavailable (due to long-term stock issues). Norethisterone for HRT is only available in combination with oestrogen. Levonorgestrel (available as the intrauterine system [IUS] Mirena®), is indicated for protection from endometrial hyperplasia during oestrogen replacement therapy,[4] but may not be of preference to some women. Options where a progestogen is required for HRT in addition to a topical oestrogen are therefore limited.
- Women vary in their tolerance to progesterone. If progestogenic adverse effects including: fluid retention, breast tenderness, headaches or migraine, mood swings, premenstrual syndrome-like symptoms, depression, acne vulgaris, lower abdominal pain, and back pain occur, the progestogen component of combined HRT may need altering.[5]
- Cyclical oral progesterone is normally given with oestrogen for the last 12-14 days of the therapeutic cycle to women with an intact uterus. This regime is recommended by the British Menopause Society (BMS) and Women's Health Concern.[6] Utrogestan® can be prescribed as 200 mg once daily for 12 days on days 15-26 of each 28 day oestrogen HRT cycle. Alternatively 100 mg can be prescribed once daily for 25 days on days 1-25 of each 28 day oestrogen HRT cycle.[7]
- In endometriosis, endometrial foci may remain despite a hysterectomy and the addition of a progesterone should be considered.
- Utrogestan® capsules (progesterone) and dydrogesterone have a neutral effect on the lipid profile, and are safer for the cardiovascular sysytem. They do not affect coagulation and have a lower risk of breast cancer compared to other progestogens.[8] Micronised progesterone results in less interaction with androgenic and mineralocorticoid receptors and has a more selective effect on progesterone receptors compared with other progestogens. Micronised progesterone can minimise the metabolic impact and side-effects associated with other progestogens.[6]

ASSESSMENT AGAINST THE ETHICAL FRAMEWORK

Evidence of Clinical Effectiveness:

For information on the use of progestogens for endometrial protection, please see the British Menopause Society tool for

clinicians, which provides a summary of clinical trial and safety data.[9]

For ease of reference the key points are summarised below:

Clinical effectiveness

Forty studies included in the systematic review by Stute et al. (2016) assessed the impact of micronised progesterone on the endometrium. Oral micronised progesterone was found to provide endometrial protection if applied sequentially for 12–14 days/ month in a dose of 200 mg/day for up to five years.

Safety

Studies have shown that continuous combined HRT is unlikely to increase the risk of endometrial cancer. The Women's Health Initiative oestrogen and progestogen study reported a neutral effect on the risk of endometrial cancer with HRT compared to placebo during the intervention phase after five years of usage of HRT (HR 0.83; 95% CI 0.49–1.40). However, a significant reduction was noted with combined oestrogen and progestogen intake compared to placebo in the post-intervention phase (HR 0.58; 95% CI 0.40–0.86) and with long term cumulative follow-up (HR 0.67; 95% CI 0.49–0.91).

In addition, the SmPC for Utrogestan® states that the reporting rate of adverse drug reactions with Utrogestan® oral and vaginal formulations was calculated as 1.43/1,000 patient year's corresponding to approximately 1.5 spontaneously reported cases in every 1,000 patients exposed to Utrogestan® (Periodic Benefit Risk Evaluation Report 01 January 2012 – 31 December 2017).[10]

Cost of treatment and Cost Effectiveness:

Medication	Dose	Unit cost*/Cost per 30 days	Cost per 28 days	Annual Cost
Utrogestan® 100 mg oral capsules	200 mg (2 x 100 mg) once daily on days 15–26 of each 28 day oestrogen HRT cycle	£5.13/30 oral capsules	£4.10	£53.44
Utrogestan® 100 mg oral capsules	100 mg once daily on days 1-25 of each 28-day oestrogen HRT cycle**	£5.13/30 oral capsules	£4.27	£55.66

*MIMS online (accessed November 2021)

** Advice from Ms Padmagirison, Consultant Obstetrician and Gynaecologist, ENHT – can also be used as a continuous daily dose without break (NB this would be off-label use).

The needs of the population

The needs of the population appear to be high. Currently no other oral cyclical progesterone is available for use in combination with a separate oestrogen product for HRT in menopausal women.

The needs of the community

There is significant prescribing of Utrogestan® currently within Hertfordshire. It is anticipated that the change to the formulary status for Utrogestan® will not increase use further.

Policy Drivers

National drivers:

NICE (NG23), 2015 – See link

- Women with vasomotor symptoms can be offered HRT and should be informed of the short-term (up to 5 years) and longer-term benefits and risks. Women with an intact uterus should be prescribed oestrogen and progestogen.

NICE CKS – See link

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

Scottish Medicines Consortium (SMC), 2009 – See link

- 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 (Utrogestan®) was as effective as another progestogen in protecting the endometrium from the hyperplastic changes associated with oestrogen therapy.
- The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.
- Micronised progesterone is the only available oral formulation of progesterone and was found to be effective in

protecting the endometrium from the hyperplastic changes associated with oestrogen therapy.

All Wales Medicines Strategy Group

- No decision on this.

Local formulary status:

- **Bedfordshire, Luton & Milton Keynes CCG**: Utrogestan® September 2021 – approved for addition to the Bedfordshire and Luton Formulary (was already on the MK Formulary) – GP initiation (Green on both Formularies).
- **North Central London Joint Formulary Committee:** Utrogestan® is restricted. Approved as progestogenic opposition for women with a uterus who require transdermal oestrogen HRT due to increased risk of VTE. This recommendation was made on the basis that combination transdermal HRT products are long-term out of stock (JFC September 2019). Not approved as progestogenic opposition for women with a uterus as part of combination oral HRT (JFC May 2018, JFC September 2019). Applicable to UCLH and Whittington Health NHS Trust. North Middlesex University Hospital, Royal Free London, Royal National Orthopaedic Hospital – Non-Formulary.
- **Buckinghamshire CCG:** Utrogestan® (100 mg, 200 mg capsules) is green, second line progesterone if 1st line Levonorgestrel Mirena® IUS is unsuitable. To be used as an adjunct to oestrogen in women with an intact uterus as HRT for management of oestrogen deficiency symptoms in peri and post-menopausal women.
- **South East London CCG:** Utrogestan® is formulary for Guy's and St Thomas' NHS Foundation Trust, Kings College Hospital, Lewisham and Greenwich NHS Trust (no traffic light status given).
- **Cambridge and Peterborough CCG**: Utrogestan® may be considered for prescribing in Primary Care where no other clinically suitable option is available due to current known shortages with HRT products. This is not recommended to be prescribed as no formal application has been made for addition to the formulary.

Equity and equality: Micronised progesterone oral capsules (Utrogestan®) for adjunctive use with oestrogen for use as HRT during menopause is indicated only in women, who are members of a protected equality group under the Equality Act 2010. The addition of Utrogestan® onto the formulary will have a positive impact for this equality group as it provides an oral treatment option. Guidance applies to all relevant patients where indicated. There is no differential impact expected on one or more equality groups differently to others: Age; Disability; Gender reassignment; Marriage & Civil Partnership; Pregnancy & Maternity; Race; Religion & Belief; Sexual orientation.

References

1. BNF. Sex hormones, oestrogens and HRT. Available at: https://bnf.nice.org.uk/treatment-summary/sex-hormones.html
2. NHS website, Hormone replacement therapy. Available at: https://www.nhs.uk/conditions/hormone-replacement-therapy-hrt/types/
3. SmPC Provera®. Available at: https://www.medicines.org.uk/emc/product/3547/smpc#gref
4. SmPC Mirena®. Available at: https://www.medicines.org.uk/emc/product/1132
5. NICE CKS. Hormone replacement therapy (HRT). Available at: https://cks.nice.org.uk/topics/menopause/prescribing-information/hormone-replacement-therapy-hrt/
6. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. Available at: https://journals.sagepub.com/doi/full/10.1177/2053369120957514
7. BNF. Available at: https://bnf.nice.org.uk/drug/progesterone.html#indicationsAndDoses
8. Primary Care Women's Health Forum. Menopause – Guidance on management and prescribing HRT for GPs. Available at: https://pcwhf.co.uk/wp-content/uploads/2021/02/Prescribing-HRT-3.pdf
9. British Menopause Society Tool for clinicians. Progestogens and endometrial protection. Available at: https://thebms.org.uk/wp-content/uploads/2021/10/14-BMS-TfC-Progestogens-and-endometrial-protection-01H.pdf
10. SmPC Utrogestan®. Available at: https://www.medicines.org.uk/emc/product/352/smpc#gref

Version	1.1 Harmonisation of Hertfordshire Medicines Management Committee (HMMC) guidance and West Essex Medicines Optimisation Programme Board (WEMOPB) guidance updates include: • Rebadging with HWE ICB and removal of ENHCCG and HVCCG headers • Review date removed and replaced with standard statement.
Developed by	HVCCG and ENHCCG PMOT
Approved by	HMMC and WEMOPB
Date approved/updated	HMMC March 2022 WEMOPB as per prescribing formulary
Review date:	The recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	1.0