Oestradiol patches now fully subsidised: what is their place in the treatment of menopausal symptoms?

Transdermal oestradiol patches (25, 50 and 100 microgram Estradot brand patches) are now fully subsidised, without the need for Special Authority approval, as a form of menopausal hormone therapy (MHT) for the treatment of menopausal symptoms. From 1 January, 2017, a 75 microgram patch will also be available.

Previously, Climara brand 50 and 100 microgram patches were available through Special Authority funding. The Special Authority funding for these medicines was removed on 1 October, 2016, and Climara brand 50 and 100 microgram patches will be delisted from 1 January, 2017. Patients who are currently using Climara patches and require ongoing treatment will need to switch to Estradot brand patches.¹

Consider MHT when menopausal symptoms are affecting a woman’s quality of life

During the menopausal transition, women have variations in menstrual cycle length and bleeding pattern. A woman is considered to be post-menopausal one year after her last menstrual period. Hormone replacement therapy for peri- or post-menopausal women is now referred to as menopausal hormone therapy (MHT) to differentiate it from hormone replacement for other endocrine conditions, e.g. growth hormone replacement.² MHT regimens consist of transdermal or oral preparations of oestrogen, alone or in combination with progestogens.

MHT can reduce hot flushes associated with menopause.² ³ ⁴

Vasomotor symptoms (hot flushes) continue to affect 45–55% of women three to four years post-menopause, and subside on average after approximately eight years.³ MHT can reduce the severity of hot flushes and reduce their frequency by 75% compared with placebo.⁴ MHT also improves other symptoms
of menopause, including sexual function, genitourinary symptoms, urinary tract infections, depressive symptoms and sleep disruption.\textsuperscript{2, 4, 7}

**Women who primarily have vaginal symptoms of menopause**, including vaginal dryness, irritation and painful intercourse can often be managed with topical (vaginal) treatments alone. Vaginal moisturisers and lubricants are appropriate as a first-line treatment.\textsuperscript{2} If symptoms are ongoing, a topical oestrogen can be trialled.\textsuperscript{2}

Lifestyle interventions that may be helpful for some women include stress reduction, weight management, smoking cessation and moderating caffeine and alcohol intake.\textsuperscript{6} Evidence is inconclusive regarding whether exercise reduces hot flushes; in some women it may help but in others it may aggravate hot flushes, and effects may differ according to the type of exercise.\textsuperscript{2, 3, 6, 14}

Non-pharmacological, dietary or supplement-based interventions have produced mixed results and do not have consistent evidence of efficacy.\textsuperscript{2, 15}

For further information on vulvovaginal changes in post-menopausal women, see: [www.bpac.org.nz/BPJ/2014/September/vulvovaginal.aspx](http://www.bpac.org.nz/BPJ/2014/September/vulvovaginal.aspx)

**Balancing the risks and benefits associated with MHT**

MHT was widely used prior to the release of the Women’s Health Initiative (WHI) study in the early 2000s.\textsuperscript{8} Prescribing then declined rapidly following documented increases in the risk of breast cancer, cardiovascular disease, stroke and mortality in women using conjugated equine oestrogens with or without medroxyprogesterone. The risks of adverse outcomes varied, depending on the woman’s age, with higher risks in women aged over 60 years, and whether oestrogen was used alone or in combination with progestogen.\textsuperscript{3, 6, 9}

The previous widespread use of MHT resulted in unacceptable risks for some women. Careful prescribing of MHT should not, however, cease completely as it is an effective treatment and some women with symptoms related to menopause are likely to gain benefit with minimal risk.\textsuperscript{3}

**Which women are likely to gain an overall benefit from MHT?**

Clinicians in primary care can consider prescribing MHT for:\textsuperscript{2, 10, 11}

1. **Women experiencing a natural menopause with symptoms affecting their quality of life**

   The use of MHT is safest in women who are aged less than 59 years or who are less than ten years post-menopause. In these women MHT may decrease the risk of cardiovascular disease and overall mortality, and the use of MHT in this age group has been described as a “window of opportunity” for maximising the benefits of MHT.\textsuperscript{3, 12, 13}

   In women aged 60–69 years, or who have been post-menopausal for ten years or more, MHT may be considered if they have symptoms which are affecting their quality of life. Menopausal symptoms typically decline over time and the risk of adverse effects increases with age, therefore older women have reduced benefit and greater risk from MHT treatment. Clinicians should first consider whether the use of other medicines or treatments to control symptoms may be more appropriate (see: “Other pharmacological treatments for menopausal symptoms”); discussion with a gynaecologist or endocrinologist may be beneficial.

   If a decision is made to initiate MHT in women aged 60-69 years, it should be used at the lowest effective dose; experts recommend transdermal rather than oral oestrogen for these women as transdermal oestrogen is associated with a lower risk of venous thromboembolism.\textsuperscript{3}

   **For women aged 70 years or over, MHT should not be initiated.**\textsuperscript{3}

2. **All women who have premature menopause due to surgery or primary ovarian insufficiency**

   Women undergoing premature menopause, i.e. prior to the age of 40 years, due to primary ovarian insufficiency or surgical induction, e.g. hysterectomy, are at increased risk of osteoporosis, cardiovascular disease and early mortality.\textsuperscript{3, 4, 16} MHT or combined hormonal contraception is recommended for these women and should be routinely offered as the benefits usually outweigh the risks.\textsuperscript{3, 16}

   Women with premature menopause may require higher doses, e.g. 100 micrograms of transdermal oestrogen, daily, to achieve the naturally occurring hormone levels in menstruating women of the same age.\textsuperscript{3, 16} The reported risks of MHT may not apply to this group of women as they are younger and typically have differing characteristics to the patients enrolled in clinical trials, e.g. a lower absolute risk of cardiovascular disease or osteoporosis.\textsuperscript{16}

**Which women should not use MHT?**

The use of oral or transdermal MHT is not recommended in women who:\textsuperscript{2, 4, 17, 18}

- Are aged 70 years or over
- Have a history of breast or endometrial cancer
- Have a moderate to high risk of breast cancer, e.g. due to family history*
Have a history of stroke, myocardial infarction, pulmonary embolism, thrombophilic disorder or venous thromboembolism; use with caution in women with a strong family history of venous thromboembolism or inherited thrombophilia - discussion with a haematologist is recommended.

- Have severe liver disease
- Have unexplained vaginal bleeding

* For example, a risk of breast cancer > 2% within the next five years. For further information and tools for calculating breast cancer risk, see: www.cancer.gov/bcrisktool/Default.aspx or ccge.medschl.cam.ac.uk/boadicea. For those women who have a family history of breast cancer but who have a risk of breast cancer <2% within the next five years, MHT should be used with caution; a low dose for as short a duration as possible is recommended.19

**Prescribing MHT**

When considering prescribing MHT, an individual risk assessment needs to be performed. Clinicians should perform a cardiovascular risk assessment and request HbA1c and liver function tests. In women with menopausal symptoms who are aged less than 45 years, follicle stimulating hormone (FSH) tests are also recommended to assess for the onset of early menopause.4

Transdermal oestrogen is likely to have fewer risks than oral oestrogen due to differing effects on markers of coagulation and inflammation, although head-to-head trials comparing the long-term effects have not been conducted.2–4 Available evidence suggests transdermal oestrogen does not increase the risk of venous thromboembolism (see: “Risks associated with MHT”) and is safer in women who have:2–4, 11, 29

- An increased risk of venous thromboembolism, e.g. BMI > 30 kg/m²
- Moderate cardiovascular risk or hypertension
- Diabetes
- Hypertriglyceridaemia
- Gallbladder disease
- Migraines
- Mild abnormalities on liver function testing

**Initiating treatment**

**Combined MHT**, i.e. oestrogen and a progestogen, is recommended for women with an intact uterus to protect the endometrium.2

**Oestrogen alone** can be used for women without a uterus.2

Initiate oestrogen at the lowest dose. A low dose of transdermal oestradiol may be easier and safer due to the difficulty of dividing tablets and cost to the patient of other formulations.

**Other pharmacological treatments for menopausal symptoms**

There are alternatives for managing menopausal symptoms for women who have contraindications to MHT use, or who prefer to avoid using MHT. However, these treatments are typically less effective than MHT and include:2, 20

- Clonidine (subsidised) – doses of 50–150 micrograms, daily, have been reported to reduce the frequency and severity of hot flushes by 26–55% compared to placebo.21–24
- Selective serotonin or serotonin-noradrenaline reuptake inhibitors (unapproved indication) – paroxetine*, citalopram, escitalopram and venlafaxine reduce hot flush frequency and severity by 27–61% compared to placebo.24
- Tibolone (unsubsidised) is a synthetic steroid with oestrogenic, progestogenic and androgenic activity. Used in doses of 2.5 mg, daily, it reduces hot flush frequency by approximately 60% compared to placebo.25 Tibolone approximately doubles the risk of stroke and is not recommended for women with a history of breast cancer as it increases the risk of cancer recurrence.26, 27 Tibolone should be used with caution in women at moderate to high risk of breast cancer, e.g. due to family history (see: “Which women should not use MHT?”).2
- Gabapentin (unapproved indication, not subsidised for the treatment of menopausal symptoms) – 900 mg, daily in divided doses, approximately halves the frequency and severity of hot flushes compared to placebo.24
- Stellate ganglion blockade is a procedure which reduces the frequency of moderate to severe hot flushes by approximately 50%.28 This is performed in some centres in New Zealand.

* Paroxetine may affect the conversion of tamoxifen to its active metabolites and the two should not be used in combination20
Options for women beginning treatment with oestrogen include:\textsuperscript{10, 20}

- 25 micrograms oestradiol transdermal patch applied twice weekly, e.g. Monday and Thursday, (fully subsidised)

- 500 micrograms oestradiol oral tablet, daily. This equates to half a tablet of the lowest strength available for many formulations and some tablets cannot be cut in half. Oestradiol valerate (Progynova) 1 mg tablets are fully subsidised but patients may have difficulty cutting these. Oestradiol 1 mg tablets (Estrofem) can be divided and are partly subsidised.

- 300 micrograms conjugated equine oestrogens oral tablet, daily, e.g. Premarin, partly subsidised

For women requiring combined oestrogen + progesterone MHT, progesterone can be prescribed as a separate formulation, an intrauterine levonorgestrel device (subsidised under Special Authority approval), which also provides contraception for women who may still be fertile, or a combination oestrogen + progesterone formulation (see: “Adding a progestogen to increase endometrial protection”).\textsuperscript{11, 20}

For further information on prescribing the progesterone component of MHT, see the NZF: www.nzf.org.nz/nzf_3858

Adverse effects of MHT

Women taking MHT may experience breast tenderness, bloating, headache and urinary incontinence; a dose reduction can be trialled to see if adverse effects resolve.\textsuperscript{6} Women using transdermal patches may experience contact sensitisation.\textsuperscript{20}

Women using cyclical MHT can be expected to have withdrawal bleeding. Unexpected vaginal bleeding, i.e. outside of expected withdrawal bleeds in women using cyclical MHT or at any time in women using continuous MHT, often occurs within three months of initiating MHT and then settles. Advise women to report any unexpected vaginal bleeding. Unexpected vaginal bleeding which begins or continues after six months of MHT use should be investigated to assess for endometrial cancer.\textsuperscript{11} Other findings associated with endometrial cancer include visible haematuria, thrombocytosis, low haemoglobin levels and high blood glucose levels.\textsuperscript{30} Patients should be referred to secondary care if endometrial cancer is suspected.

Monitoring and follow-up

Women should be followed up within one to three months of initiating MHT to assess treatment response and any adverse effects.\textsuperscript{2} Subsequent follow-up can occur every six to 12 months.\textsuperscript{2} Women using MHT should have a mammogram every two years.\textsuperscript{11}
Treatment can be titrated up or down according to clinical response, e.g. 25 microgram oestradiol patch to a 50 microgram oestradiol patch, if symptom relief is not adequate.\textsuperscript{2, 6} Measurement of serum oestradiol levels is generally not necessary but may be useful to confirm absorption if symptoms persist after increasing doses.\textsuperscript{2}

**Duration of treatment**

The appropriate duration of MHT is uncertain. Menopausal symptoms often return as MHT is withdrawn. For women who have undergone a natural menopause, the continued use of MHT treatment should be reviewed annually, taking into account the risks and benefits of continuing treatment.\textsuperscript{6, 15, 17} For women using oestrogen combined with progestogen treatment, the risk of breast cancer increases after seven years of use and progressively decreases after stopping treatment.\textsuperscript{3} It is recommended that the risks and benefits of treatment be re-evaluated if continuing use beyond five years.\textsuperscript{17}

For women who have undergone premature menopause, treatment should continue until they reach their early fifties, the average age of natural menopause, at which point a shared decision on withdrawal of treatment can be made.\textsuperscript{3, 4, 11}

Consultation with a gynaecologist is recommended if treatment is to be continued long-term.

**Withdrawing MHT**

Up to 50\% of women report the reappearance of vasomotor symptoms upon withdrawal of MHT; this is similar for women regardless of age or duration of use, suggesting that it is related to the withdrawal of treatment as opposed to the reappearance of underlying symptoms.\textsuperscript{6} Withdrawal symptoms may last for 12 months or longer.\textsuperscript{31} Women may be at greater risk of myocardial infarction if MHT is stopped before age 60 years compared to ceasing use after age 60 years, and women of any age may have a transiently increased risk of myocardial infarction and fracture after stopping MHT.\textsuperscript{10, 32}

Withdrawing treatment can be done either by stopping abruptly or by tapering the dose over weeks to months. Women who stop abruptly can experience greater initial withdrawal symptoms, however, evidence suggests there are no differences in rates of withdrawal symptoms six months after stopping MHT.\textsuperscript{4, 6}

**Patient information and videos** covering the symptoms of menopause, pharmacological and non-pharmacological management are available from the Australasian Menopause Society:

- www.menopause.org.au/for-women/information-sheets
- www.menopause.org.au/for-women/videos

---

**Acknowledgement:** Thank you to Dr Anna Fenton, Endocrinologist, Canterbury District Health Board, Immediate Past President Australasian Menopause Society and Co-Editor-in-chief Climacteric (Journal of the International Menopause Society) for expert review of this article.
References:


6 November 2016 www.bpac.org.nz