CKS safe practical clinical answers - *fast*

Advice before starting HRT

What issues should I discuss with a woman before starting HRT?

- The risks and benefits of hormone replacement therapy.
- The expected duration of treatment:
  - For vasomotor symptoms, most women require 2–3 years of treatment, but some women may need longer. This judgement should be made on a case-by-case basis with regular attempts to discontinue. Symptoms may recur for a short time after stopping HRT.
  - Topical (vaginal) oestrogen may be required long term. Regular attempts (at least annually) to stop treatment are usually made. Symptoms may recur once treatment has stopped.
- Any possible adverse effects such as breast tenderness or enlargement, nausea, headaches, or bleeding.

What advice should I give about the benefits of HRT?

- Hormone replacement therapy (HRT) is effective for:
  - Treating vasomotor symptoms (e.g. hot flushes and night sweats).
  - Treating urogenital symptoms (e.g. vaginal dryness, dyspareunia as a result of vaginal dryness, recurrent urinary tract infections, and urinary frequency and urgency).
  - Sleep or mood disturbances caused by hot flushes and night sweats.
  - Preventing osteoporosis. HRT is not normally used as a first-line treatment (as the risks outweigh the benefits) except in women with premature ovarian failure.
  - Reducing the risk of colorectal cancer (but HRT is currently not recommended for this use).

What advice should I give about the possible risks of HRT?

- There is a *small* increase in risk for:
  - Breast cancer: oestrogens may slightly increase the risk of having breast cancer diagnosed. Combined (oestrogen and progestogen) HRT increases this risk by about 1.6 times after 5 years of use and 2.3 times after 10 years of use. Risk decreases within a few years of stopping HRT.
  - Endometrial cancer: increased risk only with unopposed oestrogen. There is no increased risk with combined (oestrogen and progestogen) HRT.
  - Ovarian cancer: long-term use of oestrogen-only HRT and combined HRT may slightly increase the risk. Risk decreases after stopping HRT.
  - Venous thromboembolism (deep vein thrombosis or pulmonary embolism): the absolute risk is small and may be lower with transdermal than oral oestrogen.
  - Coronary heart disease: the increased risk is for women who have started combined HRT more than 10 years after the menopause.
  - Stroke and dementia: found mainly in women over the age of 65 years.

Prescribing HRT

How should I manage peri-menopausal women with HRT (intact uterus)?

- Offer lifestyle advice.
- Advise about the risks and benefits of hormone replacement therapy (HRT) and record in the notes.

- For urogenital symptoms (e.g. vaginal dryness, dyspareunia) offer treatment with low-dose vaginal oestrogen (cream, pessary, tablet, or ring) or combined, systemic (oral or transdermal), cyclical HRT:
  - Low-dose vaginal oestrogen may be preferred if the woman does not wish to take systemic HRT or cannot tolerate systemic HRT.
  - For women with infrequent periods or who cannot tolerate progestogens, a systemic 3-monthly regimen may be preferred.
- For vasomotor symptoms (e.g. hot flushes, night sweats), with or without urogenital symptoms offer systemic (oral or transdermal) cyclical combined HRT:
  - For women with infrequent periods or who cannot tolerate progestogens, a 3-monthly regimen may be preferred.
- Advise the woman that she may still get pregnant if contraception is not used:
  - A suitable method of contraception should be used for 1 year after the last menstrual period if the woman is more than 50 years of age, or for 2 years after the last menstrual period if the woman is less than 50 years of age.
  - See the CKS topic on Contraception for more information on contraception in perimenopausal women.

What follow up is required?

- Review the woman 3 months after starting hormone replacement therapy (HRT) and once each year thereafter.
- At 3-months:
  - Enquire about bleeding patterns, check blood pressure, and body weight.
  - Assess the effectiveness of treatment and adjust to achieve symptom control.
  - Enquire about adverse effects and manage appropriately.
- Once each year:
  - Check blood pressure, effectiveness of treatment and adjust to achieve symptom control.
  - Enquire about adverse effects and manage appropriately.
  - Consider switching from cyclical HRT to continuous combined HRT, if appropriate.
  - Interrupt treatment with intravaginal oestrogen and consider stopping systemic HRT, to re-assess the need for continued use.
  - Discuss the risks and benefits of HRT. Explain that some of the risks (e.g. breast cancer, ovarian cancer) associated with HRT increase with longer duration of HRT.
  - Perform a breast examination if indicated by personal or family history.
  - Encourage breast awareness and participation in the national breast screening programme as appropriate for their age.
  - Pelvic examination is required only if clinically indicated (e.g. if there is unscheduled bleeding, especially if heavy, prolonged, or recurrent).

When should I refer women who have started HRT?

- Refer women who are taking cyclical hormone replacement therapy if:
  - There is a change in pattern of withdrawal bleeds or break through bleeding.
  - There is multiple treatment failure e.g. three or more regimens have been tried.
- Refer to a team specializing in the management of gynaecological cancer (depending on local arrangements) any persistent or unexplained bleeding after cessation of hormone therapy for 6 weeks.

When should I switch to a continuous combined preparation?

- Consider switching from cyclical to continuous combined HRT when the woman is considered to be postmenopausal. This may be difficult to judge. Women are generally considered to be postmenopausal if:
  - They are more than 54 years of age (approximately 80% of women are postmenopausal by this age).

o They have had previous amenorrhoea or increased levels of follicle-stimulating hormone (FSH). Women who experienced 6 months of amenorrhoea or had increased FSH levels in their mid-40s are likely to be postmenopausal after taking several years of cyclical HRT.

Prescriptions

Monthly cyclical combined tablets (low dose oestrogen)

Age from 40 years onwards

Climagest (estradiol 1mg/norethisterone 1mg x12 days)
Climagest 1mg tablets Take one tablet once a day. (Take in the order shown on the packet). Supply 84 tablets.
Age: from 40 years onwards NHS cost: £16.69 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Elleste Duet (estradiol 1mg /norethisterone 1mg x12 days)
Elleste Duet 1mg tablets Take one tablet once a day. (Take in the order shown on the packet). Supply 84 tablets.
Age: from 40 years onwards NHS cost: £9.72 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Femoston (estradiol 1mg/dydrogesterone 10mg x14 days)
Femoston 1/10mg tablets Take one tablet once a day. (Take in the order shown on the packet). Supply 84 tablets.
Age: from 40 years onwards NHS cost: £13.47 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started between the first and the fifth day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Novofem (estradiol 1mg/norethisterone 1mg x12 days)
Novofem tablets Take one tablet once a day. (Take in the order shown on the packet). Supply 84 tablets.
Age: from 40 years onwards NHS cost: £13.50 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the fifth day of your period, or at any time if you are no longer having regular periods If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Prempak-C 0.625mcg (oestrogen 625mcg/norgest 150mcg x12days)
Prempak-C 0.625mg tablets Take one maroon tablet once a day. In addition, take one light brown tablet once a day for 12 days, as shown on the packet. Supply 1 3-month pack.
Age: from 40 years onwards NHS cost: £17.67 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Premique Cycle (oestrogen 625mcg/medroxyprogest 10mg x14 days)
Premique Cycle tablets Take one tablet once a day. (Take in the order shown on the packet). Supply 84 tablets.
Age: from 40 years onwards NHS cost: £24.14 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Monthly cyclical combined tablets (high dose oestrogen)

Age from 40 years onwards

Climagest (estradiol 2mg/norethisterone 1mg x12 days)
Climagest 2mg tablets Take one tablet once a day. (Take in the order shown on the packet). Supply 84 tablets.

Age: from 40 years onwards NHS cost: £16.69 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Clinorette (estradiol 2mg/norethisterone 1 mg x12 days)
Clinorette tablets Take one tablet once a day. (Take in the order shown on the packet). Supply 84 tablets.
Age: from 40 years onwards NHS cost: £9.23 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the fifth day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Elleste Duet (estradiol 2mg/norethisterone 1mg x12 days)
Elleste Duet 2mg tablets Take one tablet once a day. (Take in the order shown on the packet). Supply 84 tablets.
Age: from 40 years onwards NHS cost: £9.72 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Femoston (estradiol 2mg/dydrogesterone 10mg x14 days)
Femoston 2/10mg tablets Take one tablet once a day. (Take in the order shown on the packet). Supply 84 tablets.
Age: from 40 years onwards NHS cost: £13.47 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started

between the first and the fifth day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Nuvelle (estradiol 2mg/levonorgestrel 75mcg x12 days)
Nuvelle tablets Take one tablet once a day. (Take in the order shown on the packet). Supply 84 tablets.
Age: from 40 years onwards NHS cost: £12.87 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the fifth day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Prempak-C (oestrogen 1.25mg/norgestrel 150mcg x 12 days)
Prempak-C 1.25mg tablets Take one yellow tablet once a day. In addition, take one light brown tablet once a day for 12 days, as shown on the packet. Supply 1 3-month pack.
Age: from 40 years onwards NHS cost: £17.67 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Monthly cyclical combined patches (low dose oestrogen)

Age from 40 years onwards

FemSeven Sequi (estradiol 50mcg/levonorgest 10mcg x14 days)
FemSeven Sequi patches Apply one patch once a week to the trunk, below the waistline. Apply in the order shown. Supply 1 3-month pack.
Age: from 40 years onwards NHS cost: £37.54 Licensed use: yes
Patient information: There are two types of patches in this packet. Use the Phase 1 patches for weeks 1 and 2, and use the Phase 2 patches for weeks 3 and 4. If you have not taken HRT before, start with the Phase 1 patches between the first and the fifth day of your period, or any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these patches as soon as your previous pack of HRT is finished. For full instructions on how to use these patches please read the package insert.

Evorel Sequi (estradiol 50mcg/norethisterone 170mcg x14 days)
Evorel Sequi patches Apply one patch twice a week to the trunk, below the waistline. Apply in the order shown. Supply 24 patches.
Age: from 40 years onwards NHS cost: £30.69 Licensed use: yes
Patient information: There are two types of patches in this packet. Use the Evorel 50 patches for weeks 1 and 2, and use the Evorel Conti patches for weeks 3 and 4. If you have not taken HRT before, start with the Evorel 50 patches between the first and the fifth day of your period, or any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these patches as soon as your previous pack of HRT is finished. For full instructions on how to use these patches please read the package insert.

Fempak 40 (estradiol 40mcg/dydrogesterone 10mg x14 days)
Femapak 40 Apply one patch twice a week to the trunk, below the waistline. In addition, take one tablet once a day for 14 days, as shown on the packet. Supply 3 one-month packs.
Age: from 40 years onwards NHS cost: £22.83 Licensed use: yes
Patient information: If you have not taken HRT before, start the patches between the first and the fifth day of your period, or any time if you are no longer having regular periods Take one tablet once a day for the 14 days shown on the packet. It is important that you take the full course of 14 tablets at the right time of the month. If you are changing from a different type of HRT, start the patches as soon as your previous pack of HRT is finished. For full instructions on how to use the patches and tablets, please read the package insert.

Monthly cyclical combined patches (high dose oestrogen)

Age from 40 years onwards

Fempak 80 (estradiol 80mcg/dydrogesterone 10mg x14 days)
Femapak 80 Apply one patch twice a week to the trunk, below the waistline. In addition, take one tablet once a day for 14 days, as shown on the packet. Supply 3 one-month packs.
Age: from 40 years onwards NHS cost: £24.18 Licensed use: yes
Patient information: If you have not taken HRT before, start the patches between the first and the fifth day of your period, or any time if you are no longer having regular periods Take one tablet once a day for the 14 days shown on the packet. It is important that you take the full course of 14 tablets at the right time of the month. If you are changing from a different type of HRT, start the patches as soon as your previous pack of HRT is finished. For full instructions on how to use the patches and tablets, please read the package insert.

3 monthly cyclical combined tablets (high dose oestrogen)

Age from 40 years onwards

Tridestra (estradiol 2mg/medroxyprogesterone 20mg)
Tridestra tablets

Take one tablet once a day. (Take in the order shown on the packet). Supply 91 tablets.
Age: from 40 years onwards NHS cost: £21.40 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should be started on the fifth day of your period, or at any time if you are no longer having regular periods If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Vaginal oestrogens

Age from 40 years onwards

Estriol 0.1% cream (500mcg estriol per application)
Ovestin 0.1% cream Insert one applicatorful into the vagina each evening until improvement occurs. Then reduce to one applicatorful twice a week. Supply 15 grams.
Age: from 40 years onwards NHS cost: £4.63 Licensed use: yes
Patient information: This product may damage latex condoms and diaphragms.

Estriol 500microgram pessaries
Ortho-Gynest 500microgram pessaries Insert one pessary into the vagina each evening, until improvement occurs. Then reduce to one pessary twice a week. Supply 30 pessaries.
Age: from 40 years onwards NHS cost: £9.84 Licensed use: yes
Patient information: This product damages latex condoms and diaphragms.

Estradiol 25microgram m/r pessaries
Vagifem 25microgram vaginal tablets Insert one pessary into the vagina each evening for 2 weeks, then reduce to one pessary twice a week. Supply 30 pessaries.
Age: from 40 years onwards NHS cost: £17.60 Licensed use: yes

Estradiol 2mg vaginal ring (7.5mcg estradiol/24 hours)
Estring 2mg vaginal ring Insert one ring high into the vagina and wear continuously for 3 months. Supply 1 vaginal ring.
Age: from 40 years onwards NHS cost: £31.42 Licensed use: yes
Patient information: This ring must be replaced every 3 months.

Scenario: Postmenopausal with uterus (HRT)

Advice before starting HRT

What issues should I discuss with a woman before starting HRT?

- The risks and benefits of hormone replacement therapy or tibolone if appropriate.
- The expected duration of treatment:

o For vasomotor symptoms, most women require 2–3 years of treatment, but some women may need longer. This judgement should be made on a case-by-case basis with regular attempts to discontinue. Symptoms may recur for a short time after stopping HRT.

o Topical (vaginal) oestrogen may be required long term. Regular attempts (at least annually) to stop treatment are usually made. Symptoms may recur once treatment has stopped.

- Any possible adverse effects such as breast tenderness or enlargement, nausea, headaches, or bleeding.

What advice should I give about the benefits of HRT?

- Hormone replacement therapy (HRT) is effective for:

o Treating vasomotor symptoms (e.g. hot flushes and night sweats).

o Treating urogenital symptoms (e.g. vaginal dryness, dyspareunia as a result of vaginal dryness, recurrent urinary tract infections, and urinary frequency and urgency).

o Sleep or mood disturbances caused by hot flushes and night sweats.

o Preventing osteoporosis. HRT is not normally used as a first-line treatment (as the risks outweigh the benefits) except in women with premature ovarian failure.

o Reducing the risk of colorectal cancer (but HRT is currently not recommended for this use).

What advice should I give about the possible risks of HRT?

- There is a *small* increase in risk for:

o Breast cancer: oestrogens may slightly increase the risk of having breast cancer diagnosed. Combined (oestrogen and progestogen) HRT increases this risk by about 1.6 times after 5 years of use and 2.3 times after 10 years of use. Risk decreases within a few years of stopping HRT.

o Endometrial cancer: increased risk only with unopposed oestrogen. There is no increased risk with combined (oestrogen and progestogen) HRT.

o Ovarian cancer: long-term use of oestrogen-only HRT and combined HRT may slightly increase the risk. Risk decreases after stopping HRT.

o Venous thromboembolism (deep vein thrombosis or pulmonary embolism): the absolute risk is small and may be lower with transdermal than oral oestrogen.

o Coronary heart disease: the increased risk is for women who have started combined HRT more than 10 years after the menopause.

o Stroke and dementia: found mainly in women over the age of 65 years.

What advice should I give about the risks and benefits of tibolone?

- Tibolone is effective for treating vasomotor symptoms and reduces the risk of spine fractures. It may also improve sexual functioning.
- Tibolone is associated with a small increased risk of stroke.
- Most studies have shown a small increased risk of having endometrial cancer diagnosed with tibolone use.
- Limited data suggest that tibolone may be associated with a small increased risk of breast cancer, and that tibolone does increase the risk of breast cancer recurrence in women with a history of breast cancer.
- In younger women, the risk profile of tibolone is broadly similar to that for conventional combined hormone replacement therapy.
- For women more than about 60 years of age, the risks associated with tibolone start to outweigh the benefits because of the increased risk of stroke.

Prescribing HRT

How should I manage post-menopausal women with HRT (intact uterus)?

- Offer lifestyle advice.
- Advise the woman about the risks and benefits of oestrogen-based hormone replacement therapy (HRT) or tibolone as appropriate and record in the notes.
- For urogenital symptoms (e.g. vaginal dryness, dyspareunia) offer low-dose vaginal oestrogen (cream, pessary, tablet, or ring) or systemic (oral or transdermal) continuous combined HRT:
  - Low-dose vaginal oestrogen may be preferred if the woman does not wish to take systemic HRT or cannot tolerate systemic HRT.
- For vasomotor symptoms (e.g. hot flushes, night sweats), with or without urogenital symptoms, offer systemic (oral or transdermal) continuous combined HRT or tibolone.
- Decreased libido: consider offering tibolone (licensed use).
- Offer advice regarding contraception: a suitable method of contraception should be used for 1 year after the last menstrual period if the woman is more than 50 years of age, or for 2 years after the last menstrual period if the woman is less than 50 years of age.
  - See the CKS topic on Contraception for more information on contraception in menopausal women.

What follow up is required?

- Review the woman 3 months after starting hormone replacement therapy (HRT) and once each year thereafter.
- At 3-months:
  - Enquire about bleeding patterns, check blood pressure, and body weight.
  - Assess the effectiveness of treatment and adjust to achieve symptom control.
  - Enquire about adverse effects and manage appropriately.
- Once each year:
  - Check blood pressure, effectiveness of treatment and adjust to achieve symptom control.
  - Enquire about adverse effects and manage appropriately.
  - Consider switching from cyclical HRT to continuous combined HRT, if appropriate.
  - Interrupt treatment with intravaginal oestrogen and consider stopping systemic HRT, to re-assess the need for continued use.
  - Discuss the risks and benefits of HRT. Explain that some of the risks (e.g. breast cancer, ovarian cancer) associated with HRT increase with longer duration of HRT.
  - Perform a breast examination if indicated by personal or family history.
  - Encourage breast awareness and participation in the national breast screening programme as appropriate for their age.
  - Pelvic examination is required only if clinically indicated (e.g. if there is unscheduled bleeding, especially if heavy, prolonged, or recurrent).

When should I refer women who have started HRT?

- Refer if:
  - Breakthrough bleeding persists for more than 4–6 months after starting HRT or tibolone.
  - A bleed occurs after amenorrhoea.
  - There is multiple treatment failure e.g. three or more regimens have been tried.
- Refer to a team specializing in the management of gynaecological cancer (depending on local arrangements) any persistent or unexplained bleeding after cessation of hormone therapy for 6 weeks.

Prescriptions

Vaginal oestrogens

Age from 40 years onwards

Estriol 0.1% cream (500mcg estriol per application)

Ovestin 0.1% cream Insert one applicatorful into the vagina each evening until improvement occurs. Then reduce to one applicatorful twice a week. Supply 15 grams.
Age: from 40 years onwards NHS cost: £4.63 Licensed use: yes
Patient information: This product may damage latex condoms and diaphragms.

Estriol 500microgram pessaries
Ortho-Gynest 500microgram pessaries Insert one pessary into the vagina each evening, until improvement occurs. Then reduce to one pessary twice a week. Supply 30 pessaries.
Age: from 40 years onwards NHS cost: £9.84 Licensed use: yes
Patient information: This product damages latex condoms and diaphragms.

Estradiol 25microgram m/r pessaries
Vagifem 25microgram vaginal tablets Insert one pessary into the vagina each evening for 2 weeks, then reduce to one pessary twice a week. Supply 30 pessaries.
Age: from 40 years onwards NHS cost: £17.60 Licensed use: yes

Estradiol 2mg vaginal ring (7.5mcg estradiol/24 hours)
Estring 2mg vaginal ring Insert one ring high into the vagina and wear continuously for 3 months. Supply 1 vaginal ring.
Age: from 40 years onwards NHS cost: £31.42 Licensed use: yes
Patient information: This ring must be replaced every 3 months.

Continuous combined tablets (low dose oestrogen)

Age from 40 years onwards

Angeliq (estradiol 1mg/drospirenone 2mg)
Angeliq tablets Take one tablet daily. Supply 84 tablets.

Age: from 40 years onwards NHS cost: £25.80 Licensed use: yes

Femoston Conti (estradiol 1mg/dydrogesterone 5mg)
Femoston-conti 1mg/5mg tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £13.47 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from HRT tablets or patches, start these tablets as soon as your previous pack of HRT is finished. If you are changing from HRT that uses patches with tablets, start these tablets as soon.

Kliovance (estradiol 1mg/norethisterone 500mcg)
Kliovance tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £14.67 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from cyclical HRT (monthly bleed while on HRT), start these tablets as soon as your monthly bleed has finished.

Indivina (estradiol 1mg/medroxyprogesterone 2.5mg)
Indivina 1mg/2.5mg tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £21.49 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 3 years since you had your last period. If you are changing from continuous HRT (no monthly bleeds while on HRT), start these tablets as soon as your previous pack of HRT is finished. If you are changing from cyclical HRT (monthly bleed while on HRT) start these tablets one week after your previous pack of HRT is finished.

Indivina (estradiol 1mg/medroxyprogesterone 5mg)
Indivina 1mg/5mg tablets Take one tablet once a day. Supply 84 tablets.

Age: from 40 years onwards NHS cost: £21.49 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 3 years since you had your last period. If you are changing from continuous HRT (no monthly bleeds while on HRT), start these tablets as soon as your previous pack of HRT is finished. If you are changing from cyclical HRT (monthly bleed while on HRT) start these tablets one week after your previous pack of HRT is finished.

Premique Low Dose (oestrogen 300mcg/medroxyprogest 1.5mg)
Premique Low Dose tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £29.85 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from HRT tablets or patches, start these tablets as soon as your previous pack of HRT is finished.

Premique (oestrogen 625mcg/medroxyprogesterone 5mg)
Premique tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £27.14 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from HRT tablets or patches, start these tablets as soon as your previous pack of HRT is finished.

Continuous combined tablets (high dose oestrogen)

Age from 40 years onwards

Climesse (estradiol 2mg/norethisterone 700mcg)
Climesse tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £31.03 Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from HRT tablets or patches, start these tablets as soon as your previous pack of HRT is finished. If you are changing from HRT that uses patches with tablets, start these tablets as soon as your previous course of tablets is finished.

Elleste Duet Conti (estradiol 2mg /norethisterone 1mg)
Elleste Duet Conti tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £17.97 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from cyclical HRT (monthly bleed while on HRT), start these tablets as soon as your monthly bleed has finished.

Indivina (estradiol 2mg/medroxyprogesterone 5mg)
Indivina 2mg/5mg tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £21.49 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 3 years since you had your last period. If you are changing from continuous HRT (no monthly bleeds while on HRT), start these tablets as soon as your previous pack of HRT is finished. If you are changing from cyclical HRT (monthly bleed while on HRT) start these tablets one week after your previous pack of HRT is finished.

Kliofem (estradiol 2mg/norethisterone 1mg)
Kliofem tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £11.43 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from cyclical HRT (monthly bleed while on HRT), start these tablets as soon as your monthly bleed has finished.

Nuvelle Continuous (estradiol 2mg/norethisterone 1mg)

Nuvelle Continuous tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £16.85 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from cyclical HRT (monthly bleed while on HRT), start these tablets as soon as your monthly bleed has finished.

Continuous combined patches (low dose oestrogen)

Age from 40 years onwards

FemSeven Conti (estradiol 50mcg/levonorgest 7mcg/24 hour)
FemSeven Conti patches Apply one patch once a week to the trunk, below the waistline. Supply 12 patches.
Age: from 40 years onwards NHS cost: £44.12 Licensed use: yes
Patient information: If you have not taken HRT before, start the patches between the first and the fifth day of your period, or any time if you are no longer having regular periods. If you are changing from a different type of HRT, start the patches as soon as your previous pack of HRT is finished. For full instructions on how to use these patches, please read the package insert.

Evorel Conti (estradiol 50mcg/norethisterone 170mcg/24 hour)
Evorel Conti patches Apply one patch twice a week to the trunk, below the waistline. Supply 24 patches.
Age: from 40 years onwards NHS cost: £35.99 Licensed use: yes
Patient information: If you have not taken HRT before, start the patches between the first and the fifth day of your period, or any time if you are no longer having regular periods. If you are changing from a different type of HRT, start the patches as soon as your previous pack of HRT is finished. For full instructions on how to use these patches, please read the package insert.

Tibolone tablets

Age from 40 years onwards

Tibolone tablets: 2.5mg once a day
Tibolone 2.5mg tablets Take one tablet once a day. Supply 84 tablets.

Age: from 40 years onwards NHS cost: £32.31 Licensed use: yes
Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from cyclical HRT (monthly bleed while on HRT), start these tablets as soon as your monthly bleed has finished.

Menopause - Management

Scenario: Menopausal symptoms after a hysterectomy (HRT):

Advice about HRT

What issues should I discuss with a woman before starting HRT?

- The risks and benefits of hormone replacement therapy.
- The expected duration of treatment:
  - For vasomotor symptoms, most women require 2–3 years of treatment, but some women may need longer. This judgement should be made on a case-by-case basis with regular attempts to discontinue. Symptoms may recur for a short time after stopping HRT.
  - Topical (vaginal) oestrogen may be required long term as symptoms recur once treatment has stopped.
- Any possible adverse effects such as breast tenderness or enlargement, nausea, headaches.

What advice should I give about the benefits of HRT?

- Hormone replacement therapy (HRT) is effective for:
  - Treating vasomotor symptoms (e.g. hot flushes and night sweats).
  - Treating urogenital symptoms (e.g. vaginal dryness, dyspareunia as a result of vaginal dryness, recurrent urinary tract infections, and urinary frequency and urgency).
  - Sleep or mood disturbances caused by hot flushes and night sweats.
  - Preventing osteoporosis. HRT is not normally used as a first-line treatment (as the risks outweigh the benefits) except in women with premature ovarian failure.
  - Reducing the risk of colorectal cancer (but HRT is currently not recommended for this use).

What advice should I give about the possible risks of HRT?

- There is a *small* increase in risk for:
  - Ovarian cancer: long-term use of oestrogen-only Hormone replacement therapy (HRT) may slightly increase the risk. Risk decreases after stopping HRT.
  - Venous thromboembolism (deep vein thrombosis or pulmonary embolism): the absolute risk is small and may be lower with transdermal than oral oestrogen.
  - Stroke and dementia: this is mainly found in women over the age of 65 years.

Prescribing HRT

How should I manage women who have had a hysterectomy with HRT?

- Offer lifestyle advice.
- Advise the woman about the risks and benefits of oestrogen-based hormone replacement therapy (HRT) and record in the notes.
- For urogenital symptoms (e.g. vaginal dryness, dyspareunia) offer low-dose vaginal oestrogen (cream, pessary, tablet, or ring) or systemic (oral or transdermal) oestrogen replacement therapy:
  - Vaginal oestrogen may be preferred if the woman does not wish to take, or cannot tolerate systemic oestrogen.
- For vasomotor symptoms (e.g. hot flushes, night sweats), with or without urogenital symptoms, offer systemic (oral, or transdermal) unopposed oestrogen replacement therapy.
- Decreased libido: seek specialist advice if considering testosterone patches or implants.

Are there any specific issues I should consider in a woman who has had a subtotal hysterectomy?

- A remnant of endometrial tissue may be present in women who have had a subtotal hysterectomy (in which the main part of the uterus is removed but the cervix is retained).
- To test for the presence of endometrial tissue, prescribe a 3-month course of cyclical hormone replacement therapy (HRT):
  - If withdrawal bleeding occurs, endometrial tissue is present, and combined HRT should be started.
  - If the woman does not have withdrawal bleeding, endometrial tissue is unlikely to be present, and oestrogen-only HRT may be started.

What follow up is required?

- Review 3 months after starting hormone replacement therapy (HRT) and once each year thereafter.
- At 3-months:
  - Check blood pressure, body weight, and assess the effectiveness of treatment; adjust HRT to achieve symptom control.
  - Enquire about any adverse effects and manage appropriately.
- Once each year:
  - Check blood pressure, effectiveness of treatment and adjust to achieve symptom control.
  - Enquire about adverse effects and manage appropriately.
  - Re-assess the need for continuing HRT.
  - Discuss the risks and benefits of HRT. Explain that some of the risks (e.g. ovarian cancer) associated with oestrogen-only HRT increase with longer duration of HRT. The risk decreases after stopping HRT.
  - Perform a breast examination if indicated by personal or family history.
  - Encourage breast awareness and participation in the national breast screening programme as appropriate for their age.

When should I refer women who have started HRT?

- Refer to secondary care if there is multiple treatment failure (e.g. three or more regimens have been tried).

Prescriptions

Oestrogen only tablets (low dose)

Age from 40 years onwards

Climaval tablets (estradiol 1mg)

Climaval 1mg tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £9.19 Licensed use: yes

Elleste Solo tablets (estradiol 1mg)
Elleste Solo 1mg tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £5.34 Licensed use: yes

Hormonin tablets (estradiol + estriol + estrone)
Hormonin tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £6.61 Licensed use: yes

Premarin tablets (conjugated oestrogen 625 micrograms)
Premarin 625microgram tablets Take one tablet daily. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £9.72 Licensed use: yes

Progynova tablets (estradiol 1mg)
Progynova 1mg tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £6.56 Licensed use: yes

Zumenon tablets (estradiol 1mg)
Zumenon 1mg tablets Take one tablet once a day. Supply 84 tablets.
Age: from 40 years onwards NHS cost: £6.89 Licensed use: yes

Oestrogen only tablets (high dose)

Age from 40 years onwards

Bedol tablets (estradiol 2mg)

Bedol 2mg tablets
Take one tablet daily.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £5.07
Licensed use: yes

Climaval tablets (estradiol 2mg)

Climaval 2mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £9.19
Licensed use: yes

Elleste Solo tablets (estradiol 2mg)

Elleste Solo 2mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £5.34
Licensed use: yes

Hormonin tablets (estradiol + estriol + estrone)

Hormonin tablets
Take two tablets once a day.
Supply 180 tablets.

Age: from 40 years onwards
NHS cost: £13.22
Licensed use: yes

Premarin tablets (conjugated oestrogen 1.25mg)

Premarin 1.25mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £13.19
Licensed use: yes

Progynova tablets (estradiol 2mg)

Progynova 2mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £7.72
Licensed use: yes

Zumenon tablets (estradiol 2mg)

Zumenon 2mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £6.89
Licensed use: yes

Oestrogen only patches (start doses)

Age from 40 years onwards

Elleste Solo MX 40 patch (estradiol 40mcg): apply twice a week

Elleste Solo MX 40 transdermal patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £15.57
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estraderm MX 50 patch (estradiol 50mcg): apply twice a week

Estraderm MX 50 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £17.22
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estradot patch (estradiol 50mcg): apply twice a week

Estradot 50micrograms/24hours patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patch.

Age: from 40 years onwards
NHS cost: £15.66
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Evorel 50 patch (estradiol 50mcg): apply twice a week

Evorel 50 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £9.72
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Fematrix 40 patch (estradiol 40mcg): apply twice a week

Fematrix 40 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £14.85
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

FemSeven 50 patch (estradiol 50mcg): apply once a week

FemSeven 50 patches
Apply one patch once a week to the trunk, below the waistline.
Supply 12 patches.

Age: from 40 years onwards
NHS cost: £18.07
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed once a week, on the same day each week. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Progynova 50 patch (estradiol 50mcg): apply once a week

Progynova TS 50 patches
Apply one patch once a week to the trunk, below the waistline.
Supply 12 patches.

Age: from 40 years onwards
NHS cost: £16.71
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed once a week, on the same day each week. When you

change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Oestrogen only patches (high dose)

Age from 40 years onwards

Estraderm MX 75 patch (estradiol 75mcg): apply twice a week
Estraderm MX 75 patches Apply one patch twice a week to the trunk, below the waistline. Supply 24 patches.
Age: from 40 years onwards NHS cost: £18.25 Licensed use: yes
Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estradot patch (estradiol 75mcg): apply twice a week
Estradot 75micrograms/24hours patches Apply one patch twice a week to the trunk, below the waistline. Supply 24 patch.
Age: from 40 years onwards NHS cost: £18.09 Licensed use: yes
Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Evorel 75 patch (estradiol 75mcg): apply twice a week
Evorel 75 patches Apply one patch twice a week to the trunk, below the waistline. Supply 24 patches.
Age: from 40 years onwards NHS cost: £11.10 Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the
same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

FemSeven 75 patch (estradiol 75mcg): apply once a week

FemSeven 75 patches
Apply one patch once a week to the trunk, below the waistline.
Supply 12 patches.

Age: from 40 years onwards
NHS cost: £17.46
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed once a week, on the same day each week. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Elleste Solo MX 80 patch (estradiol 80mcg): apply twice a week

Elleste Solo MX 80 transdermal patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £17.97
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Fematrix 80 patch (estradiol 80mcg): apply twice a week

Fematrix 80 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £18.00
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the
same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estraderm MX 100 patch (estradiol 100mcg): apply twice a week
Estraderm MX 100 patches Apply one patch twice a week to the trunk, below the waistline. Supply 24 patches.
Age: from 40 years onwards NHS cost: £18.94 Licensed use: yes
Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estradot patch (estradiol 100mcg): apply twice a week
Estradot 100micrograms/24hours patches Apply one patch twice a week to the trunk, below the waistline. Supply 24 patch.
Age: from 40 years onwards NHS cost: £18.93 Licensed use: yes
Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Evorel 100 patch (estradiol 100mcg):apply twice a week
Evorel 100 patches Apply one patch twice a week to the trunk, below the waistline. Supply 24 patches.
Age: from 40 years onwards NHS cost: £11.52 Licensed use: yes
Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

FemSeven 100 patch (estradiol 100mcg): apply twice a week
FemSeven 100 patches Apply one patch once a week to the trunk, below the waistline. Supply 12 patches.

Age: from 40 years onwards
NHS cost: £18.21
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed once a week, on the same day each week. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Progynova TS 100 patch (estradiol 100mcg): apply once a week

Progynova TS 100 patches
Apply one patch once a week to the trunk, below the waistline.
Supply 12 patches.

Age: from 40 years onwards
NHS cost: £19.68
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed once a week, on the same day each week. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Oestrogen only patches (low dose)

Age from 40 years onwards

Estraderm MX 25 patch (estradiol 25mcg): apply twice a week

Estraderm MX 25 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £17.15
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put
the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estraderm TTS 25 patch (estradiol 25mcg): apply twice a week

Estraderm TTS 25 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £22.36
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estradot patch (estradiol 25mcg): apply twice a week

Estradot 25micrograms/24hours patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patch.

Age: from 40 years onwards
NHS cost: £15.60
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Evorel 25 patch (estradiol 25mcg): apply twice a week

Evorel 25 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £8.58
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put
the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estradot patch (estradiol 37.5mcg): apply twice a week

Estradot 37.5micrograms/24hours patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patch.

Age: from 40 years onwards
NHS cost: £15.60
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Other non-oral oestrogens

Age from 40 years onwards

Estradiol 0.06% gel: apply once a day
Oestrogel Pump-Pack 0.06% gel Apply two measures once a day to the arms, shoulders or inner thighs as directed. Supply 240 grams.
Age: from 40 years onwards NHS cost: £7.39 Licensed use: yes
Patient information: Apply the gel to a clean, dry, unbroken area of skin using the template provided The area covered should be twice the size of the template. Apply one measure (half the dose) to each arm, shoulder or thigh. Do not apply the gel on or near the breasts or the vulval region. Let the gel dry for 5 minutes before covering with clothing. Avoid skin contact with another person (especially men), and avoid using other skin products or washing the area for an hour after application. The dose may be increased if necessary (after at least 1 months trial) to 3 or 4 measures once a day.

Estradiol 0.1% gel sachets: apply once a day
Sandrena 1mg gel sachets Apply the contents of one sachet once a day to the lower trunk or thighs as directed. Supply 84 1mg sachets.
Age: from 40 years onwards NHS cost: £18.24 Licensed use: yes
Patient information: Apply the gel to intact areas of skin such as the lower trunk or thighs, using the right and left sides on alternate days. Wash hands after application. Not to be applied on the breasts or face and avoid contact with eyes. Allow area of application to dry for 5 minutes and do not wash area for at least 1 hour. After 2 to 3 months, the dose can be reduced or increased if necessary.

Estradiol 25mg implant
Estradiol 25mg implant For subcutaneous implantation. Supply 1 implant.
Age: from 40 years onwards NHS cost: £9.59 Licensed use: yes
Patient information: This implant will be put in by the doctor or the nurse.

Estradiol 50mg implant
Estradiol 50mg implant For subcutaneous implantation. Supply 1 implant.
Age: from 40 years onwards NHS cost: £19.16 Licensed use: yes
Patient information: This implant will be put in by the doctor or the nurse.

Vaginal oestrogens

Age from 40 years onwards

Ortho-Gynest 500microgram pessaries
Insert one pessary into the vagina each evening, until improvement occurs. Then reduce to one pessary twice a week. Supply 30 pessaries.
Age: from 40 years onwards NHS cost: £9.84 Licensed use: yes
Patient information: This product damages latex condoms and diaphragms.

Estradiol 25microgram m/r pessaries
Vagifem 25microgram vaginal tablets Insert one pessary into the vagina each evening for 2 weeks, then reduce to one pessary twice a week. Supply 30 pessaries.
Age: from 40 years onwards NHS cost: £17.60 Licensed use: yes

Estradiol 2mg vaginal ring (7.5mcg estradiol/24 hours)
Estring 2mg vaginal ring Insert one ring high into the vagina and wear continuously for 3 months. Supply 1 vaginal ring.
Age: from 40 years onwards NHS cost: £31.42 Licensed use: yes
Patient information: This ring must be replaced every 3 months.

Menopause - Management

Scenario: Premature menopause

Advice for women before starting HRT

What issues should I discuss with a woman before starting HRT?

- The risks and benefits of hormone replacement therapy (HRT).
- The expected duration of treatment:
  - Women with premature menopause usually take HRT up to the age of the natural menopause (50 years); at that time, treatment is usually reassessed.
  - Topical (vaginal) oestrogen may be required long term. Regular attempts (at least annually) to stop treatment are usually made. Symptoms may recur once treatment has stopped.
- Any possible adverse effects such as breast tenderness or enlargement, nausea, headaches, or bleeding.

What advice should I give about the benefits of HRT?

- Hormone replacement therapy (HRT) is effective for:
  - Treating vasomotor symptoms (e.g. hot flushes and night sweats).

o Treating urogenital symptoms (e.g. vaginal dryness, dyspareunia as a result of vaginal dryness, recurrent urinary tract infections, and urinary frequency and urgency).

o Sleep or mood disturbances caused by hot flushes and night sweats.

o Preventing osteoporosis. HRT is not normally used as a first-line treatment (as the risks outweigh the benefits) except in women with premature ovarian failure.

o Reducing the risk of colorectal cancer (but HRT is currently not recommended for this use).

What advice should I give about the possible risks of HRT?

- There is a *small* increase in risk for:

o Breast cancer: oestrogens may slightly increase the risk of having breast cancer diagnosed. Combined (oestrogen and progestogen) HRT increases this risk by about 1.6 times after 5 years of use and 2.3 times after 10 years of use. Risk decreases within a few years of stopping HRT.

o Endometrial cancer: increased risk only with unopposed oestrogen. There is no increased risk with combined (oestrogen and progestogen) HRT.

o Ovarian cancer: long-term use of oestrogen-only HRT and combined HRT may slightly increase the risk. Risk decreases after stopping HRT.

o Venous thromboembolism (deep vein thrombosis or pulmonary embolism): the absolute risk is small and may be lower with transdermal than oral oestrogen.

o Coronary heart disease: the increased risk is for women who have started combined HRT more than 10 years after the menopause.

o Stroke and dementia: found mainly in women over the age of 65 years.

Management

How can I manage women with a premature menopause?

- Offer lifestyle advice.

- Refer women who are younger than 40 years of age to a gynaecologist.

- Offer systemic hormone replacement therapy (HRT) or the combined oral contraceptive pill (COC):

o HRT: the HRT regimens used will depend on whether or not the woman has undergone a hysterectomy, still has some ovarian activity and still has periods.

o For women who are still having periods offer oral or transdermal, combined cyclical HRT (a 3-monthly regimen may be preferred).

o For women who have had a hysterectomy offer oral or transdermal oestrogen replacement therapy.

o COC: whether or not the woman can be prescribed the COC will depend upon the woman's age and associated risk factors (e.g. smoking).

- Decreased libido: testosterone implants and patches may be considered (especially in oophorectomized women); however, seek specialist advice before prescribing.

- Advise the woman that she may still become pregnant if contraception is not used.

o See the CKS topic on Contraception for a detailed discussion on the use of contraception in perimenopausal women.

When should I consider stopping HRT?

- Women with premature menopause usually take hormone replacement therapy up to the age of the natural menopause (50 years); at that time, treatment is usually reassessed.

What follow-up is required?

Review 3 months after starting hormone replacement therapy (HRT) and once each year thereafter.

- At 3-months:
  - Check blood pressure, body weight, and assess the effectiveness of treatment; adjust HRT to achieve symptom control.
  - Enquire about any adverse effects and manage appropriately.
- Once each year:
  - Check blood pressure, effectiveness of treatment and adjust to achieve symptom control.
  - Enquire about adverse effects and manage appropriately.
  - Interrupt treatment with intravaginal oestrogen to re-assess the need for continued use.
  - Discuss the risks and benefits of HRT. Explain that some of the risks (e.g. ovarian cancer) associated with oestrogen-only HRT increase with longer duration of HRT. The risk decreases after stopping HRT.
  - Perform a breast examination if indicated by personal or family history.
  - Encourage breast awareness and participation in the national breast screening programme as appropriate for their age.
  - Pelvic examination is required only if clinically indicated (e.g. if there is unscheduled bleeding, especially if heavy, prolonged, or recurrent).

When should I refer a women with premature menopause who has started HRT?

- For women taking cyclical hormone replacement therapy (HRT) refer if:
  - There is a change in pattern of withdrawal bleeds or breakthrough bleeding.
- For women taking continuous combined HRT or long cycle regimens refer if:
  - Breakthrough bleeding persists for more than 4–6 months after starting therapy.
  - A bleed occurs after amenorrhoea.
- Refer if there is multiple treatment failure e.g. three or more regimens have been tried.
- Refer to a team specializing in the management of gynaecological cancer (depending on local arrangements) any persistent or unexplained bleeding after cessation of hormone therapy for 6 weeks.

Prescriptions

Monthly cyclical combined tablets (low dose oestrogen)

Age from 40 years onwards

Climagest (estradiol 1mg/norethisterone 1mg x12 days)

Climagest 1mg tablets
Take one tablet once a day. (Take in the order shown on the packet).
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £16.69

Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Elleste Duet (estradiol 1mg /norethisterone 1mg x12 days)

Elleste Duet 1mg tablets
Take one tablet once a day. (Take in the order shown on the packet).
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £9.72
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Femoston (estradiol 1mg/dydrogesterone 10mg x14 days)

Femoston 1/10mg tablets
Take one tablet once a day. (Take in the order shown on the packet).
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £13.47
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started between the first and the fifth day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Novofem (estradiol 1mg/norethisterone 1mg x12 days)

Novofem tablets
Take one tablet once a day. (Take in the order shown on the packet).
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £13.50
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the fifth day of your period, or at any time if you are no longer having regular periods If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Prempak-C 0.625mcg (oestrogen 625mcg/norgest 150mcg x12days)

Prempak-C 0.625mg tablets
Take one maroon tablet once a day. In addition, take one light brown tablet once a day for 12 days, as shown on the packet.
Supply 1 3-month pack.

Age: from 40 years onwards
NHS cost: £17.67
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Premique Cycle (oestrogen 625mcg/medroxyprogest 10mg x14 days)

Premique Cycle tablets
Take one tablet once a day. (Take in the order shown on the packet).

Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £24.14
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Monthly cyclical combined tablets (high dose oestrogen)

Age from 40 years onwards

Climagest (estradiol 2mg/norethisterone 1mg x12 days)

Climagest 2mg tablets
Take one tablet once a day. (Take in the order shown on the packet).
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £16.69
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Clinorette (estradiol 2mg/norethisterone 1 mg x12 days)

Clinorette tablets
Take one tablet once a day. (Take in the order shown on the packet).
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £9.23
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the fifth day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Elleste Duet (estradiol 2mg/norethisterone 1mg x12 days)

Elleste Duet 2mg tablets
Take one tablet once a day. (Take in the order shown on the packet).
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £9.72
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Femoston (estradiol 2mg/dydrogesterone 10mg x14 days)

Femoston 2/10mg tablets
Take one tablet once a day. (Take in the order shown on the packet).
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £13.47
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started between the first and the fifth day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Nuvelle (estradiol 2mg/levonorgestrel 75mcg x12 days)

Nuvelle tablets
Take one tablet once a day. (Take in the order shown on the packet).
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £12.87
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the fifth day of your period, or at any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Prempak-C (oestrogen 1.25mg/norgestrel 150mcg x 12 days)

Prempak-C 1.25mg tablets
Take one yellow tablet once a day. In addition, take one light brown tablet once a day for 12 days, as shown on the packet.
Supply 1 3-month pack.

Age: from 40 years onwards
NHS cost: £17.67
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the first day of your period, or at any time if you are no longer having regular periods If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Monthly cyclical combined patches (low dose oestrogen)

Age from 40 years onwards

FemSeven Sequi (estradiol 50mcg/levonorgest 10mcg x14 days)

FemSeven Sequi patches
Apply one patch once a week to the trunk, below the waistline. Apply in the order shown.
Supply 1 3-month pack.

Age: from 40 years onwards
NHS cost: £37.54
Licensed use: yes

Patient information: There are two types of patches in this packet. Use the Phase 1 patches for weeks 1 and 2, and use the Phase 2 patches for weeks 3 and 4. If you have not taken HRT before, start with the Phase 1 patches between the first and the fifth day of your period, or any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these patches as soon as your previous pack of HRT is finished. For full instructions on how to use these patches please read the package insert.

Evorel Sequi (estradiol 50mcg/norethisterone 170mcg x14 days)

Evorel Sequi patches
Apply one patch twice a week to the trunk, below the waistline. Apply in the order shown.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £30.69
Licensed use: yes

Patient information: There are two types of patches in this packet. Use the Evorel 50 patches for weeks 1 and 2, and use the Evorel Conti patches for weeks 3 and 4. If you have not taken HRT before, start with the Evorel 50 patches between the first and the fifth day of your period, or any time if you are no longer having regular periods. If you are changing from a different type of HRT, start these patches as soon as your previous pack of HRT is finished. For full instructions on how to use these patches please read the package insert.

Fempak 40 (estradiol 40mcg/dydrogesterone 10mg x14 days)

Femapak 40
Apply one patch twice a week to the trunk, below the waistline. In addition, take one tablet once a day for 14 days, as shown on the packet.
Supply 3 one-month packs.

Age: from 40 years onwards
NHS cost: £22.83
Licensed use: yes

Patient information: If you have not taken HRT before, start the patches between the first and the fifth day of your period, or any time if you are no longer having regular periods Take one tablet once a day for the 14 days shown on the packet. It is important that you take the full course of 14 tablets at the right time of the month. If you are changing from a different type of HRT, start the patches as soon as your previous pack of HRT is finished. For full instructions on how to use the patches and tablets, please read the package insert.

Monthly cyclical combined patches (high dose oestrogen)

Age from 40 years onwards

Fempak 80 (estradiol 80mcg/dydrogesterone 10mg x14 days)

Femapak 80
Apply one patch twice a week to the trunk, below the waistline. In addition, take one tablet once a day for 14 days, as shown on the packet.
Supply 3 one-month packs.

Age: from 40 years onwards
NHS cost: £24.18
Licensed use: yes

Patient information: If you have not taken HRT before, start the patches between the first and the fifth day of your period, or any time if you are no longer having regular periods Take one tablet once a day for the 14 days shown on the packet. It is important that you take the full course of 14 tablets at the right time of the month. If you are changing from a different type of HRT, start the patches as soon as your previous pack of HRT is finished. For full instructions on how to use the patches and tablets, please read the package insert.

3 monthly cyclical combined tablets (high dose oestrogen)

Age from 40 years onwards

Tridestra (estradiol 2mg/medroxyprogesterone 20mg)

Tridestra tablets
Take one tablet once a day. (Take in the order shown on the packet).
Supply 91 tablets.

Age: from 40 years onwards
NHS cost: £21.40
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should be started on the fifth day of your period, or at any time if you are no longer having regular periods If you are changing from a different type of HRT, start these tablets as soon as your previous pack of HRT is finished.

Continuous combined tablets (low dose oestrogen)

Age from 40 years onwards

Angeliq (estradiol 1mg/drospirenone 2mg)

Angeliq tablets
Take one tablet daily.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £25.80
Licensed use: yes

Femoston Conti (estradiol 1mg/dydrogesterone 5mg)

Femoston-conti 1mg/5mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £13.47
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from HRT tablets or patches, start these tablets as soon as your previous pack of HRT is finished. If you are changing from HRT that uses patches with tablets, start these tablets as soon as your previous course of tablets is finished.

Kliovance (estradiol 1mg/norethisterone 500mcg)

Kliovance tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £14.67
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from cyclical HRT (monthly bleed while on HRT), start these tablets as soon as your monthly bleed has finished.

Indivina (estradiol 1mg/medroxyprogesterone 2.5mg)

Indivina 1mg/2.5mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £21.49
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 3 years since you had your last period. If you are changing from continuous HRT (no monthly bleeds while on HRT), start these tablets as soon as your previous pack of HRT is finished. If you are changing from cyclical HRT (monthly bleed while on HRT) start these tablets one week after your previous pack of HRT is finished.

Indivina (estradiol 1mg/medroxyprogesterone 5mg)

Indivina 1mg/5mg tablets

Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £21.49
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 3 years since you had your last period. If you are changing from continuous HRT (no monthly bleeds while on HRT), start these tablets as soon as your previous pack of HRT is finished. If you are changing from cyclical HRT (monthly bleed while on HRT) start these tablets one week after your previous pack of HRT is finished.

Premique Low Dose (oestrogen 300mcg/medroxyprogest 1.5mg)

Premique Low Dose tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £29.85
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from HRT tablets or patches, start these tablets as soon as your previous pack of HRT is finished.

Premique (oestrogen 625mcg/medroxyprogesterone 5mg)

Premique tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £27.14
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from HRT tablets or patches, start these tablets as soon as your previous pack of HRT is finished.

Continuous combined tablets (high dose oestrogen)

Age from 40 years onwards

Climesse (estradiol 2mg/norethisterone 700mcg)

Climesse tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £31.03
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from HRT tablets or patches, start these tablets as soon as your previous pack of HRT is finished. If you are changing from HRT that uses patches with tablets, start these tablets as soon as your previous course of tablets is finished.

Elleste Duet Conti (estradiol 2mg /norethisterone 1mg)

Elleste Duet Conti tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £17.97
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from cyclical HRT (monthly bleed while on HRT), start these tablets as soon as your monthly bleed has finished.

Indivina (estradiol 2mg/medroxyprogesterone 5mg)

Indivina 2mg/5mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £21.49
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 3 years since you had your last period. If you are changing from continuous HRT (no monthly bleeds while on HRT), start these tablets as soon as your previous pack of HRT is finished. If you are changing from cyclical HRT (monthly bleed while on HRT) start these tablets one week after your previous pack of HRT is finished.

Kliofem (estradiol 2mg/norethisterone 1mg)

Kliofem tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £11.43
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from cyclical HRT (monthly bleed while on HRT), start these tablets as soon as your monthly bleed has finished.

Nuvelle Continuous (estradiol 2mg/norethisterone 1mg)

Nuvelle Continuous tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £16.85
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from cyclical HRT (monthly bleed while on HRT), start these tablets as soon as your monthly bleed has finished.

Continuous combined patches (low dose oestrogen)

Age from 40 years onwards

FemSeven Conti (estradiol 50mcg/levonorgest 7mcg/24 hour)

FemSeven Conti patches
Apply one patch once a week to the trunk, below the waistline.
Supply 12 patches.

Age: from 40 years onwards
NHS cost: £44.12
Licensed use: yes

Patient information: If you have not taken HRT before, start the patches between the first and the fifth day of your period, or any time if you are no longer having regular periods. If you are changing from a different type of HRT, start the patches as soon as your previous pack of HRT is finished. For full instructions on how to use these patches, please read the package insert.

Evorel Conti (estradiol 50mcg/norethisterone 170mcg/24 hour)

Evorel Conti patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £35.99
Licensed use: yes

Patient information: If you have not taken HRT before, start the patches between the first and the fifth day of your period, or any time if you are no longer having regular periods. If you are changing from a different type of HRT, start the patches as soon as your previous pack of HRT is finished. For full instructions on how to use these patches, please read the package insert.

Tibolone tablets

Age from 40 years onwards

Tibolone tablets: 2.5mg once a day

Tibolone 2.5mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £32.31
Licensed use: yes

Patient information: If you have not taken HRT before, these tablets should not be used unless it is more than 12 months since you had your last period. If you are changing from cyclical HRT (monthly bleed while on HRT), start these tablets as soon as your monthly bleed has finished.

Oestrogen only tablets (low dose)

Age from 40 years onwards

Climaval tablets (estradiol 1mg)

Climaval 1mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £9.19
Licensed use: yes

Elleste Solo tablets (estradiol 1mg)

Elleste Solo 1mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £5.34
Licensed use: yes

Hormonin tablets (estradiol + estriol + estrone)

Hormonin tablets

Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £6.61
Licensed use: yes

Premarin tablets (conjugated oestrogen 625 micrograms)

Premarin 625microgram tablets
Take one tablet daily.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £9.72
Licensed use: yes

Progynova tablets (estradiol 1mg)

Progynova 1mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £6.56
Licensed use: yes

Zumenon tablets (estradiol 1mg)

Zumenon 1mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £6.89
Licensed use: yes

Oestrogen only tablets (high dose)

Age from 40 years onwards

Bedol tablets (estradiol 2mg)

Bedol 2mg tablets
Take one tablet daily.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £5.07
Licensed use: yes

Climaval tablets (estradiol 2mg)

Climaval 2mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £9.19
Licensed use: yes

Elleste Solo tablets (estradiol 2mg)

Elleste Solo 2mg tablets
Take one tablet once a day.

Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £5.34
Licensed use: yes

Hormonin tablets (estradiol + estriol + estrone)

Hormonin tablets
Take two tablets once a day.
Supply 180 tablets.

Age: from 40 years onwards
NHS cost: £13.22
Licensed use: yes

Premarin tablets (conjugated oestrogen 1.25mg)

Premarin 1.25mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £13.19
Licensed use: yes

Progynova tablets (estradiol 2mg)

Progynova 2mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £7.72
Licensed use: yes

Zumenon tablets (estradiol 2mg)

Zumenon 2mg tablets
Take one tablet once a day.
Supply 84 tablets.

Age: from 40 years onwards
NHS cost: £6.89
Licensed use: yes

Oestrogen only patches (start doses)

Age from 40 years onwards

Elleste Solo MX 40 patch (estradiol 40mcg): apply twice a week

Elleste Solo MX 40 transdermal patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £15.57
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and

Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estraderm MX 50 patch (estradiol 50mcg): apply twice a week

Estraderm MX 50 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £17.22
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estradot patch (estradiol 50mcg): apply twice a week

Estradot 50micrograms/24hours patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patch.

Age: from 40 years onwards
NHS cost: £15.66
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Evorel 50 patch (estradiol 50mcg): apply twice a week

Evorel 50 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £9.72
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Fematrix 40 patch (estradiol 40mcg): apply twice a week

Fematrix 40 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £14.85
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip,

abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

FemSeven 50 patch (estradiol 50mcg): apply once a week

FemSeven 50 patches
Apply one patch once a week to the trunk, below the waistline.
Supply 12 patches.

Age: from 40 years onwards
NHS cost: £18.07
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed once a week, on the same day each week. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Progynova 50 patch (estradiol 50mcg): apply once a week

Progynova TS 50 patches
Apply one patch once a week to the trunk, below the waistline.
Supply 12 patches.

Age: from 40 years onwards
NHS cost: £16.71
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed once a week, on the same day each week. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Oestrogen only patches (high dose)

Age from 40 years onwards

Estraderm MX 75 patch (estradiol 75mcg): apply twice a week

Estraderm MX 75 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £18.25
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estradot patch (estradiol 75mcg): apply twice a week

Estradot 75micrograms/24hours patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patch.

Age: from 40 years onwards

NHS cost: £18.09
Licensed use: yes
Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Evorel 75 patch (estradiol 75mcg): apply twice a week

Evorel 75 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £11.10
Licensed use: yes
Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

FemSeven 75 patch (estradiol 75mcg): apply once a week

FemSeven 75 patches
Apply one patch once a week to the trunk, below the waistline.
Supply 12 patches.

Age: from 40 years onwards
NHS cost: £17.46
Licensed use: yes
Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed once a week, on the same day each week. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Elleste Solo MX 80 patch (estradiol 80mcg): apply twice a week

Elleste Solo MX 80 transdermal patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £17.97
Licensed use: yes
Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Fematrix 80 patch (estradiol 80mcg): apply twice a week

Fematrix 80 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £18.00
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estraderm MX 100 patch (estradiol 100mcg): apply twice a week

Estraderm MX 100 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £18.94
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estradot patch (estradiol 100mcg): apply twice a week

Estradot 100micrograms/24hours patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patch.

Age: from 40 years onwards
NHS cost: £18.93
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Evorel 100 patch (estradiol 100mcg):apply twice a week

Evorel 100 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £11.52
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

FemSeven 100 patch (estradiol 100mcg): apply twice a week

FemSeven 100 patches

Apply one patch once a week to the trunk, below the waistline.
Supply 12 patches.

Age: from 40 years onwards
NHS cost: £18.21
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed once a week, on the same day each week. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Progynova TS 100 patch (estradiol 100mcg): apply once a week

Progynova TS 100 patches
Apply one patch once a week to the trunk, below the waistline.
Supply 12 patches.

Age: from 40 years onwards
NHS cost: £19.68
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed once a week, on the same day each week. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Oestrogen only patches (low dose)

Age from 40 years onwards

Estraderm MX 25 patch (estradiol 25mcg): apply twice a week

Estraderm MX 25 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £17.15
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estraderm TTS 25 patch (estradiol 25mcg): apply twice a week

Estraderm TTS 25 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £22.36
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and

Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estradot patch (estradiol 25mcg): apply twice a week

Estradot 25micrograms/24hours patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patch.

Age: from 40 years onwards
NHS cost: £15.60
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Evorel 25 patch (estradiol 25mcg): apply twice a week

Evorel 25 patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patches.

Age: from 40 years onwards
NHS cost: £8.58
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

Estradot patch (estradiol 37.5mcg): apply twice a week

Estradot 37.5micrograms/24hours patches
Apply one patch twice a week to the trunk, below the waistline.
Supply 24 patch.

Age: from 40 years onwards
NHS cost: £15.60
Licensed use: yes

Patient information: Stick one patch onto a clean, dry, hairless area of skin below the waist. The buttocks are often the best place to stick patches. Patches can also be stuck on the lower back, hip, abdomen or upper thigh. Never put a patch on or near the breasts. The patch needs to be changed twice a week. It is usually easier to change your patch on the same days each week e.g. Monday and Thursday. When you change your patch, always put the new patch on a fresh area of skin. For full instructions on how to use these patches, please read the package insert.

What should I do if there is poor symptom control?

- Review the woman:
  - Check that the hormone replacement therapy (HRT) has been used as recommended for at least 3 months to ensure full effect.
  - Check that patches are adherent.
  - Review the woman's expectations. HRT can help symptoms due to oestrogen deficiency but is not an answer to all problems.
  - Consider an alternative diagnosis. See Other causes of the symptoms.
- Treatment options include:
  - Increasing the oestrogen dose.
  - Adding vaginal oestrogen if urogenital symptoms are not controlled.
  - Switching from oral to a non-oral route (e.g. if absorption is poor owing to a bowel disorder or if a drug interaction is present).
  - Switching delivery system if patch adhesion is poor.

Menopause - Management

Scenario: Managing adverse effects of HRT

CKS safe practical clinical answers - *fast*

How do I manage oestrogen-related adverse effects?

- Oestrogen-related adverse effects (e.g. fluid retention, bloating, breast tenderness or enlargement, nausea, headaches, leg cramps, and dyspepsia) may occur continuously or randomly throughout the cycle.
- Advise to persist with treatment for 3 months (as adverse effects may resolve):
  - Leg cramps: lifestyle changes (e.g. exercise and stretching of the calf muscles) may be helpful.
  - Nausea/gastric upset: adjust the timing of the oestrogen dosage or take with food.
  - Breast tenderness: low-fat, high-carbohydrate diet may be helpful.
  - Migraine: transdermal therapy as this produces more stable oestrogen levels.
- For persistent adverse effects, consider:
  - Reducing the dosage *or*
  - Changing the oestrogen type (i.e. swap between the two main forms of oestrogen, that is, estradiol and conjugated oestrogens) *or*
  - Changing the route of delivery (e.g. tablets may cause nausea, but patches and gels generally do not).

In depth

How do I manage progestogen-related adverse effects (other than bleeding)?

- Progestogen-related adverse effects (e.g. fluid retention, breast tenderness, headaches/migraine, mood swings, depression, acne, lower abdominal pain, and backache) tend to occur in a cyclical pattern during the progestogen phase of cyclical HRT.

- Advise the woman to persist with therapy for 3 months (adverse effects may resolve).
- For persistent symptoms, consider:
  - Changing froma a more androgenic progestogen (e.g. norethisterone and norgestrel) to a less androgenic progestogen (e.g. medroxyprogesterone or dydrogesterone).
  - Changing from oral to transdermal, vaginal, or intrauterine progestogen.
  - Reducing the duration of progestogen administration: swap from a 14 day to a 12 day product.
  - Changing to a product with a lower dose of progestogen (dosages are preparation dependent).
  - Switching to a long-cycle regimen, where progestogen is given for 14 days every 3 months (only suitable for women without natural regular periods).
  - Changing to continuous combined therapy or tibolone (only suitable if postmenopausal).
- Many of these strategies are the opposite of what may be needed to give better bleeding control.

In depth

How do I manage bleeding on monthly cyclical regimens?

- Before changing treatment, visualize the cervix, check smears are up to date, and refer for transvaginal ultrasound to exclude pelvic abnormalities.
- Check compliance, drug interactions (e.g. anticonvulsants), or gastrointestinal upset.
- Altering the progestogen part of the regimen may improve bleeding problems:
  - Heavy or prolonged bleeding: increase the duration or dosage of the progestogen, or change the type of progestogen. Idiopathic menorrhagia may be helped by using the levonorgestrel-releasing intrauterine system combined with an oestrogen delivered orally or transdermally.
  - Bleeding early in the progestogen phase: increase dosage or change the type of progestogen.
  - Irregular bleeding: change regimen or increase the dosage of progestogen.
  - No bleeding whilst taking a cyclical regimen reflects an atrophic endometrium and occurs in 5% of women. Pregnancy needs to be excluded in perimenopausal women. Check compliance if the progestogen component is taken separately.

How do I manage bleeding on continuous combined or during long cycle HRT regimens?

- Irregular breakthrough bleeding or spotting is common in the first 3–6 months.
- Bleeding beyond 6 months or after a spell of amenorrhoea requires further investigation or referral.

How do I manage weight gain?

- Reassure the woman that HRT does not cause significant weight gain.

Menopause - Management

Scenario: Stopping HRT

When should I consider stopping HRT?

- If systemic Hormone replacement therapy (HRT) is being used for symptom control consider a trial withdrawal (if a woman is symptom-free) after 1–2 years.
  - Advise the woman that symptoms may recur for a short time once HRT is stopped.
  - Counsel the woman about the possible risks of HRT if she wishes to continue treatment, particularly if treatment is being used for longer than 5 years.
- Topical (vaginal) oestrogen may be required long term as symptoms can recur once treatment has stopped.
  - Stop treatment at least annually to re-assess the need for continued treatment.
- Women with premature menopause usually take hormone replacement therapy up to the age of the natural menopause (50 years); at that time, therapy is reassessed. Some women will still be symptomatic.

In depth

How should HRT be stopped?

- Some women do not notice any symptoms even with abrupt cessation of hormone replacement therapy (HRT), while others may experience a recurrence of hot flushes and sweats.
- Some experts suggest that HRT should be gradually reduced rather than stopped abruptly. Suggested strategies are:
  - **Oestrogen-only tablets:** reduce from a 2 mg to a 1 mg tablet for 1–2 months, then use 1 mg on alternate days for a further 1–2 months.
  - **Oestrogen-only patches:** reduce the dose gradually to 25 micrograms daily (e.g. step the dose down a patch strength each month). Half a matrix-type patch (12.5 micrograms daily) can be used for a further 1–2 months.
  - **Cyclical combined HRT tablets:** reduce to a cyclical HRT pack containing 1 mg estradiol for 1–2 months. Cut the tablet in half for the next 1–2 months; this will ensure that the woman still receives oestrogen combined with a progestogen.
  - **Cyclical combined HRT patches:** reduce the dose as for oestrogen-only patches, but ensure that the woman still uses the oestrogen-only patches for 2 weeks of the cycle followed by the combined patches for a further 2 weeks, to ensure endometrial protection.
  - **Continuous combined HRT tablets or patches:** reduce the dose gradually every 1–2 months to the lowest strength tablet or patch. Then, take half a tablet or patch daily for a further 1–2 months.
- If symptoms are severe after HRT is stopped or persist for several months after stopping, the woman may wish to restart HRT after reassessment and counselling. Often a lower dose of HRT can be used (e.g. estradiol 1 mg) if HRT is restarted.

Menopause - Management

Scenario: Managing the menopause without HRT

CKS safe practical clinical answers - *fast*

How can I manage menopausal symptoms without HRT?

- Offer lifestyle advice to control symptoms; if this is not effective, consider other treatments.
- For vasomotor symptoms, consider:

- A trial (2 weeks) of paroxetine (20 mg daily), fluoxetine (20 mg daily), citalopram (20 mg daily), or venlafaxine 37.5 mg twice a day (unlicensed).
- A trial (2–4 weeks) of clonidine 50 to 75 micrograms twice a day (licensed use).
- A progestogen such as norethisterone or megestrol (both unlicensed). Seek specialist advice.

- For vaginal dryness, prescribe a vaginal lubricant or moisturizer, such as Replens MD®.
- Manage psychological symptoms, such as mood disturbances, anxiety, and depression on an individual basis. They may be addressed using self-help groups, psychotherapy, other forms of counselling, or antidepressants.
- CKS does not recommend the use of complementary therapies (e.g. soy, red clover, black cohosh).

What follow up is required?

- Advise the woman to return if:
  - Lifestyle measures alone have been of insufficient benefit or her symptoms have worsened.
  - She does not respond to antidepressant treatment within 2 weeks.
  - Clonidine was started and her symptoms have not improved in 4 weeks, or she is experiencing adverse effects, such as dizziness or constipation.
- Review all women at least annually.

When should I consider stopping treatment?

- Consider stopping treatment if a woman is symptom-free on treatment; a trial withdrawal can be undertaken after 1–2 years of treatment.
- Advise that symptoms sometimes recur once treatment is stopped.
- Use of vaginal moisturizers and lubricants may be continued indefinitely.

Prescriptions

Antidepressants

Age from 25 years onwards

Citalopram tablets: 20mg once a day

Citalopram 20mg tablets
Take one tablet once a day.
Supply 14 tablets.

Age: from 25 years onwards
NHS cost: £0.65
Licensed use: no - off-label indication

Fluoxetine capsules: 20mg once a day

Fluoxetine 20mg capsules
Take one capsule once a day.
Supply 14 capsules.

Age: from 25 years onwards
NHS cost: £0.32
Licensed use: no - off-label indication

Paroxetine tablets: 20mg once a day

Paroxetine 20mg tablets
Take one tablet once a day.
Supply 14 tablets.

Age: from 25 years onwards

NHS cost: £2.84
Licensed use: no - off-label indication

Venlafaxine tablets: 37.5mg twice a day

Venlafaxine 37.5mg tablets
Take one tablet twice a day.
Supply 28 tablets.

Age: from 25 years onwards
Licensed use: no - off-label indication

Clonidine

Age from 25 years onwards

Clonidine tablets: 50 micrograms twice a day

Clonidine 25microgram tablets
Take two tablets twice a day.
Supply 112 tablets.

Age: from 25 years onwards
NHS cost: £14.92
Licensed use: yes

Clonidine tablets: 75 micrograms twice a day

Clonidine 25microgram tablets
Take three tablets twice a day.
Supply 168 tablets.

Age: from 25 years onwards
NHS cost: £22.38
Licensed use: yes

Menopause - Management
detailed answers

Overview of management

- **Assess the stage of the menopause** to determine whether the woman is perimenopausal, postmenopausal, or has a premature menopause (less than 45 years of age).
- **Assess the symptoms and their severity:** (e.g. hot flushes, night sweats, vaginal dryness).
- **Refer women if they:**
  - Present with clinical features suggestive of cervical or endometrial cancer.
  - Are less than 40 years of age at presentation.
  - Would like hormone replacement therapy (HRT) but have a contraindication to it (e.g. current of past breast or endometrial cancer).
- Offer lifestyle advice to *all* women with menopausal symptoms.
- Offer treatment with (HRT) if, the woman has been given advice about the risks and benefits of HRT, has no contraindications to HRT and would like treatment. See:
  - Peri-menopausal management with HRT.
  - Post-menopausal management with HRT.
  - Management with HRT after hysterectomy.

- **Offer alternative treatments** with antidepressants or clonidine if HRT is inappropriate, see Management without HRT.
- **Offer HRT or the combined oral contraceptive pill** if the woman is younger than 45 years old, see Management of premature menopause.

How should I assess a woman with menopausal symptoms?

- **Assess the stage of the menopause:**
  - Ask the woman if she is still having periods, to determine whether she is perimenopausal or postmenopausal:
  - If her periods have stopped, record when the last period occurred.
  - If the woman is still having periods, ask about their frequency, heaviness, and duration.
  - Determine if the woman is less than 45 years of age (premature menopause):
  - See Management of premature menopause.
- **Assess the symptoms and their severity:**
  - Ask which symptoms the woman has, to determine if they would be likely to respond to hormone replacement therapy (HRT) (e.g. hot flushes, night sweats, vaginal dryness), or whether other treatments may be more suitable (e.g. treatment for primary depression or primary insomnia).
  - Determine the severity of the symptoms and the extent to which they are affecting the woman's life.
- **Assess the risk of cardiovascular disease:**
  - Women with cardiovascular disease or at increased risk of cardiovascular disease should have their cardiovascular risk factors managed — see the CKS topic on CVD risk assessment and management.
- **Assess the risk of osteoporosis:**
  - See the CKS topic on Osteoporosis - treatment.
- **Discuss the woman's expectations:**
  - Ask why she has consulted (e.g. concern regarding the cause of the symptoms).
  - Ask if she would like treatment for her symptoms.
- **Assess what type of treatment may be appropriate:**
  - Ask the woman if she would like treatment with HRT or without HRT.
  - For women who would like HRT, check that they are suitable for treatment:
  - Ask if they have any contraindications to HRT (e.g. history of breast cancer, venous thromboembolism).
  - Discuss the risks and benefits of HRT.
  - Record body mass index and blood pressure.
  - Breast examination is not *routinely* necessary, however the national mammography screening programme and personal breast awareness must be discussed before starting HRT.
  - Pelvic examination is not *routinely* required unless clinically indicated (past or current disease, symptoms, or family history).
  - Investigations are not routinely indicated.
  - See Managing symptoms with HRT.
  - For women who are not suitable for treatment with HRT (e.g. those who have contraindications to HRT) or do not want to use HRT, see Managing symptoms without HRT.

- Encourage all women to participate in the national cervical screening programme.

Clarification / Additional information

- The following are all contraindications to starting hormone replacement therapy:
  - Hormone-dependent cancer (e.g. endometrial cancer, current or past breast cancer).
  - Active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction).
  - Venous thromboembolic disease, pulmonary embolism, or current pregnancy.
  - Severe active liver disease.
  - Undiagnosed breast mass.
  - Uninvestigated abnormal vaginal bleeding.
- Investigations are not routinely indicated before starting hormone replacement therapy unless:
  - There is sudden change in menstrual pattern, intermenstrual bleeding, postcoital bleeding, or postmenopausal bleeding: consider doing an endometrial assessment.
  - There is a personal or family history of venous thromboembolism: consider doing a thrombophilia screen.
  - There is a high risk of breast cancer: mammography or MRI may be considered (as appropriate for the woman's age).
  - For more information see the current NICE guidance on Familial breast cancer.
  - The woman has arterial disease or a high load of other risk markers for arterial disease: a lipid profile may be useful.

Basis for recommendation

- These recommendations are based on pragmatic advice, published expert opinion from review articles, and standard textbooks [Korhonen et al, 1997; Working Group on Breast and Pelvic Examination, 2001; RCOG, 2004; AACE Menopause Guidelines Revision Task Force, 2006; Grady, 2006; Monga, 2006; Rees and Purdie, 2006a; Roberts, 2007].

When should I refer?

- Refer urgently if the woman presents with clinical features suggestive of cervical or endometrial cancer:
  - Abnormal bleeding (postcoital bleeding, unscheduled vaginal bleeding, especially if heavy, prolonged, or recurrent or a sudden change in menstrual pattern).
  - Postmenopausal bleeding.
  - Persistent intermenstrual bleeding and negative pelvic examination.
  - A palpable abdominal or pelvic mass (refer urgently for ultrasonography).
- Refer to secondary care women:
  - Who are less than 40 years of age at presentation.
- Seek specialist advice if a woman would like hormone replacement therapy but has a contraindication to it:
  - Hormone-dependent cancer (e.g. endometrial cancer, current or past breast cancer).
  - Active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction).
  - Venous thromboembolic disease, pulmonary embolism.

- Current pregnancy.
- Severe active liver disease.
- Undiagnosed breast mass.
- Uninvestigated abnormal vaginal bleeding.

Basis for recommendation

- These recommendations are based on published expert opinion [Waller and McPherson, 2003; Monga, 2006; Rees and Purdie, 2006b].
- The National Institute for Health and Clinical Excellence recommends urgent referral for all women presenting with alarm symptoms of gynaecological cancer [NICE, 2005].
- Women who are less than 40 years of age require investigations to determine the cause of a premature menopause (e.g. primary ovarian failure) and to discuss fertility if appropriate.

What lifestyle advice can I give for menopausal symptoms?

- Encourage all women to make lifestyle modifications to reduce menopausal symptoms:
  - Hot flushes and night sweats:
  - Take regular exercise, wear lighter clothing, sleep in a cooler room, and reduce stress.
  - Avoid possible triggers, such as spicy foods, caffeine, smoking, and alcohol.
  - Sleep disturbances:
  - Avoiding exercise late in the day and maintaining a regular bedtime can improve sleep.
  - Mood and anxiety disturbances:
  - Adequate sleep, regular physical activity, and relaxation exercises may help.
  - Cognitive symptoms:
  - Exercise and good sleep hygiene may improve subjective cognitive symptoms.

Basis for recommendation

- These recommendations are based on published expert opinion [ICSI, 2006; Rees and Purdie, 2006a].
- There is evidence that smoking cigarettes and having a body mass index of more than 30 kg/m^2 increases the likelihood of flushing.
- From observational studies, there are more reports of positive effects of exercise on hot flushes than reports of negative effects or mixed findings. Therefore, regular exercise might positively influence the frequency and severity of vasomotor symptoms in menopausal women [Daley et al, 2006].

How should I manage menopausal symptoms with HRT?

What issues should I discuss with a woman before starting HRT?

- Before starting hormone replacement therapy (HRT), discuss:
  - The benefits and possible risks of hormone replacement therapy or tibolone (if appropriate).
  - The expected duration of therapy:

o For vasomotor symptoms, most women require 2–3 years of therapy, but some women may need longer. This judgement should be made on a case-by-case basis with regular attempts to discontinue. Symptoms may recur for a short time after stopping HRT [MHRA and CHM, 2007b].

o Topical (vaginal) oestrogen may be required long term. In some women symptoms may recur once treatment has stopped [Rees and Purdie, 2006a].

o Women with premature menopause usually take hormone replacement therapy up to the age of the natural menopause (50 years); at that time, therapy is usually reassessed.

o Any possible adverse effects, such as breast tenderness or enlargement, nausea, headaches, or bleeding.

What advice should I give about the benefits of HRT?

- Advise the woman that hormone replacement therapy (HRT) is effective for:

o Treating vasomotor symptoms (e.g. hot flushes and night sweats).

o Treating urogenital symptoms (e.g. vaginal dryness, dyspareunia as a result of vaginal dryness, recurrent urinary tract infections, and urinary frequency and urgency).

o Sleep or mood disturbances caused by hot flushes and night sweats.

o Preventing osteoporosis. HRT is not normally used as a first-line treatment (as the risks outweigh the benefits) except in women with premature ovarian failure.

o Reducing the risk of colorectal cancer (but hormone replacement therapy is currently not recommended for this use).

Basis for recommendation

- These recommendations are based on expert opinion from the published literature, as well as systematic reviews and large randomized controlled trials [NZGG, 2004; BMS, 2006a; ICSI, 2006; Rees and Purdie, 2006a; MHRA and CHM, 2007b].

- **Hot flushes and night sweats:**

o Good evidence indicates that oral, or transdermal hormone replacement therapy (HRT), used as oestrogen alone or oestrogens combined with progestogens, is highly effective for reducing the frequency and severity of hot flushes and night sweats caused by the menopause.

- **Vaginal atrophy (dryness and dyspareunia):**

o There is evidence that HRT preparations (combined oral and transdermal oestrogens and progestogens, or intravaginal oestrogens) are effective for treating vaginal atrophy (dryness, burning and itching, and dyspareunia).

- **Recurrent urinary tract infections:**

o There is evidence that oral and intravaginal oestrogen is effective for preventing urinary tract infections. The appropriate dose and duration of therapy have not been established. Long-term treatment may be required because symptoms recur when treatment is stopped [Rees and Purdie, 2006a].

- **Sleep disturbances:**

o By alleviating night sweats, HRT often improves sleep. Women often report an improvement in sleep patterns with HRT even if hot flushes or night sweats are not prominent menopausal symptoms [ICSI, 2006]. There is evidence that combined oral oestrogen and progestogen therapy provides a small statistical but not clinically meaningful improvement in sleep disturbances.

- **Incontinence:**

o The British Menopause Society currently recommends the use of systemic or topical oestrogen for urinary frequency and urgency [BMS, 2006a]. The evidence to support the use of oestrogens is conflicting. A Cochrane systematic review found evidence that oestrogen treatment improved or cured incontinence; this was more likely with urge incontinence [Moehrer et al, 2003]. However, a subsequently published analysis of the Women's Health

Initiative trial found that oestrogen therapy alone and combined with progestogen therapy increased the risk of urinary incontinence among continent women and worsened urinary incontinence among symptomatic women after 1 year [Hendrix et al, 2005].

- **Mood disorders:**

o No evidence indicates that HRT has a direct effect on mood, irritability, or anxiety. However, HRT may be helpful if other menopausal symptoms, such as hot flushes and sleep disturbance, are present [ICSI, 2006].

- **Libido:**

o Other than relieving hot flushes and improving sleep, HRT improves urogenital atrophy, thinning, dryness, and loss of elasticity, all of which may cause dyspareunia. While this may improve sexual functioning for many women, HRT has no proven direct benefit on sexuality or libido [ICSI, 2006].

- **Osteoporosis:**

o There is evidence that HRT reduces the risk of both spine and hip as well as other osteoporotic fractures. A few years treatment with HRT around the time of menopause may have a long term effect on fracture reduction [Writing Group for the Women's Health Initiative Investigators, 2002; Women's Health Initiative, 2004].

- **Colorectal cancer:**

o There is evidence that HRT reduces the risk of colorectal cancer [Writing Group for the Women's Health Initiative Investigators, 2002].

o The risk of colorectal cancer increases with increasing age. Therefore, HRT produces a greater potential reduction in the number of cases of colorectal cancer in older women than in younger women. However, some of the potential risks of HRT also increase with age. Little is known about colorectal cancer risk when treatment is stopped. No information is available about HRT in high-risk populations, and current evidence does not allow recommendation of HRT to prevent colorectal cancer [BMS, 2006a].

- Use of HRT may be associated with reduced tooth loss, reduced incidence of age-related macular degeneration and cataracts, improved faecal continence, improved wound healing, and improved balance. However, HRT is not licensed for these indications, and the risks of prescribing HRT for any of these problems are likely to outweigh the benefits.

What advice should I give about the possible risks of HRT?

- Advise the woman that there is a *small* increase in risk for:

o Breast cancer.

o Endometrial cancer.

o Ovarian cancer.

o Venous thromboembolism (deep vein thrombosis or pulmonary embolism).

o Coronary heart disease for women who have started combined therapy more than 10 years after menopause.

o Stroke.

Clarification / Additional information

- The number of additional cases (compared with the background risk) of cancer and cardiovascular conditions in hormone replacement therapy users is discussed in Risks of HRT.

Basis for recommendation

- The Medicines and Healthcare products Regulatory Agency (MHRA) and its independent adviser, the Commission on Human Medicines, have reviewed the safety data for hormone replacement therapy

(HRT). The above recommendations are based on this safety review [MHRA and CHM, 2007b]. The MHRA found the following:

o **Breast cancer:**

o Combined HRT has been associated with the highest risk. The risk is lower with oestrogen-only HRT than with combined HRT.

o Risk increases with duration of use and returns to baseline within 5 years of stopping treatment.

o **Endometrial cancer:**

o In women with a uterus, oestrogen-only HRT substantially increases the risk of endometrial hyperplasia and carcinoma in a dose- and duration-dependent manner.

o Addition of progestogen cyclically for at least 10 days per 28-day cycle greatly reduces the risk, and addition of progestogen every day eliminates the risk.

o **Ovarian cancer:**

o Long-term use of oestrogen-only or combined HRT may be associated with a small increased risk of ovarian cancer. This risk returns to baseline a few years after stopping treatment.

o **Venous thromboembolism (deep vein thrombosis or pulmonary embolism):**

o The risk is higher with combined HRT than with oestrogen-only HRT, and events are more likely in the first year of use.

o The level of risk associated with other routes of administration has not been clearly established, although it may be lower with transdermal HRT.

o **Stroke:**

o In randomized controlled trials, oestrogen-only and combined HRT increased the risk of stroke (mostly ischaemic) compared with placebo. Although the increase in relative risk seems to be similar irrespective of age, baseline risk of stroke increases with age and therefore older women have a greater absolute risk. Limited observational data suggest that this risk may depend on oestrogen dose.

o **Cognitive effects:**

o There is evidence that for women who start HRT after 65 years of age, conjugated equine oestrogen does not protect against mild cognitive impairment or probable dementia. Evidence suggests that combined HRT (conjugated equine oestrogen and medroxyprogesterone acetate) may increase the risk of dementia in women more than 75 years of age. The MHRA have advised that HRT not be prescribed for preventing a decline in cognitive function [CSM, 2004a].

▪ **Coronary heart disease (CHD):**

o No increased risk of CHD with the use of oestrogen-only HRT has been identified to date. Importantly, there are no data from randomized controlled trials to suggest a cardiovascular benefit with oestrogen-only or combined HRT [MHRA and CHM, 2007b].

o Randomized controlled trials have found an increased risk of CHD in women who started combined (oestrogen-progestogen) therapy more than 10 years after menopause. Very few randomized controlled trials have assessed younger, newly menopausal women, and some have suggested a lower relative risk in these women compared with older women. The low baseline risk of CHD in most younger women, and the very low attributable risk due to HRT, means that their overall CHD risk is likely to be low.

o For a more detailed discussion on the role of hormone replacement therapy and coronary heart disease in women see the website for the MHRA.

What advice should I give about the risks and benefits of tibolone?

▪ Advise the woman that tibolone is effective for treating vasomotor symptoms and reduces the risk of spine fractures. It may also improve sexual functioning.

▪ Tibolone is associated with a small increased risk of stroke.

- Most studies have shown a small increased risk of having endometrial cancer diagnosed with tibolone use.
- Limited data suggest that tibolone may be associated with a small increased risk of breast cancer, and that tibolone does increase the risk of breast cancer recurrence in women with a history of breast cancer.
- In younger women, the risk profile of tibolone is broadly similar to that for conventional combined hormone replacement therapy.
- For women more than about 60 years of age, the risks associated with tibolone start to outweigh the benefits because of the increased risk of stroke.

Basis for recommendation

- These recommendations are based on randomized controlled trials and a recently published assessment of the benefit–risk balance published by the Medicines and Healthcare products Regulatory Agency (MHRA) [MHRA and CHM, 2007a; MHRA, 2009].
- The MRHA assessed the balance of benefits and risks for tibolone after the Long-term Intervention on Fractures with Tibolone (LIFT) study was terminated because of an increased risk of stroke in those assigned tibolone compared with those assigned placebo. The main results of this assessment were as follows:

o **Stroke:**

o The LIFT study identified a significantly (2.2-times) increased risk of stroke, mostly ischaemic, in tibolone users; risk increased from the first year of treatment. Baseline risk of stroke is strongly age-dependent, and the absolute risk with tibolone therefore increases with older age.

o Randomized controlled trials have identified an approximate 1.3-times increase in stroke risk with combined hormone replacement therapy (HRT).

o **Breast cancer:**

o There are limited clinical trial data for breast cancer risk in healthy women. However, the LIBERATE study in women with previous breast cancer was stopped because it could not establish non-inferiority of tibolone compared with placebo.

o The Million Women Study identified a significantly increased risk of breast cancer in tibolone users (relative risk [RR] 1.5, 95% CI 1.3 to 1.7), which is similar to that for oestrogen-only HRT (RR 1.3, 95% CI 1.2 to 1.4) and significantly lower than that for combined HRT (RR 2.0, 95% CI 1.9 to 2.1). Risk increased with longer duration of use and returned to baseline within a few years of stopping treatment.

o **Venous thromboembolism:**

o The few data available do not suggest an increased risk of venous thromboembolism compared with combined HRT users or with non-users.

o **Coronary heart disease:**

o No conclusions can be drawn from the available data. In view of the increased risk of stroke associated with tibolone, an increase in coronary events is biologically plausible. In studies, tibolone caused a marked dose-dependent decrease in high-density lipoprotein cholesterol levels (–22.4% after 2 years); total triglyceride and lipoprotein (a) levels were also reduced. A decrease in total cholesterol and very low-density lipoprotein cholesterol levels was not dose dependent, and low-density lipoprotein cholesterol levels did not change. The clinical implication of these findings is not yet known.

- **Endometrial cancer:** The MHRA have reviewed the evidence on effects of tibolone on the endometrium and have concluded that:

o Most studies show an increased risk of having endometrial cancer diagnosed associated with use of tibolone.

o Despite the lack of evidence for an association between tibolone and endometrial cancer from pharmacological studies and the 2 year Tibolone Histology of the Endometrium and Breast Endpoints Study (THEBES), two large epidemiological studies have identified a significant increase in the risk of endometrial cancer in association with tibolone use that increased with increasing duration of use. A higher incidence of endometrial cancer was reported in older women given tibolone in the LIFT study compared with placebo. These women also experienced an increase in incidence of endometrial double wall thickness, measured by vaginal ultrasonography, compared with placebo.

o Although a causal relation has not been proven, women who are prescribed tibolone have an increased risk of having endometrial cancer diagnosed than both never-users and users of combined HRT. The reason for this increase is not clear.

▪ For more detailed information, see the MHRA website.

How should I manage perimenopausal women with HRT (intact uterus)?

How should I manage peri-menopausal women with HRT (intact uterus)?

▪ Offer lifestyle advice.

▪ Advise about the risks and benefits of hormone replacement therapy (HRT) and record this in her notes.

▪ **Urogenital symptoms alone** (e.g. vaginal dryness, dyspareunia, recurrent urinary tract infections, or urinary frequency and urgency):

o Offer treatment with low-dose vaginal oestrogen (cream, pessary, tablet, or ring) *or* systemic (oral or transdermal) cyclical combined HRT:

o Low-dose vaginal oestrogen may be preferred if the woman does not wish to take systemic HRT or cannot tolerate systemic HRT.

o For women with infrequent periods or who cannot tolerate progestogens, a 3-monthly regimen may be preferred.

▪ **Vasomotor symptoms** (e.g. hot flushes, night sweats) with or without urogenital symptoms:

o Offer systemic (oral or transdermal) cyclical combined HRT:

o For women with infrequent periods or who cannot tolerate progestogens, a 3-monthly regimen may be preferred.

▪ For a full discussion on the choice of HRT preparations, see Type of product to offer.

▪ Advise the woman that she may still become pregnant if contraception is not used:

o A suitable method of contraception should be used for 1 year after the last menstrual period if the woman is more than 50 years of age, or for 2 years after the last menstrual period if the woman is less than 50 years of age.

o See the CKS topic on Contraception for a detailed discussion on the most appropriate method of contraception in perimenopausal women and for how long it should be continued.

Clarification / Additional information

▪ Prescribe hormone replacement therapy at the lowest effective dose for the shortest duration possible.

▪ Maximal benefit of systemic hormone replacement therapy is usually seen within 3 months, and treatment is generally continued for up to 5 years.

▪ Urogenital symptoms: topical oestrogens should be used in the lowest effective amount to minimize systemic absorption. Treatment should be interrupted as least annually to re-assess the need for continued treatment. If breakthrough bleeding or spotting appears at any time on therapy, the

reason should be investigated and may include endometrial biopsy to exclude endometrial malignancy. Long term treatment is often required as symptoms can recur on cessation of therapy.

Basis for recommendation

- These recommendations are based on published expert opinion and evidence from systematic reviews and large randomized controlled trials [NZGG, 2004; ICSI, 2006; Rees and Purdie, 2006a; SOGC, 2006; MHRA and CHM, 2007b].

- **Vaginal oestrogens:**

o Low-dose oestrogen therapy is preferred because it incurs no adverse endometrial effects and a progestogen is not required for endometrial protection [Rees and Purdie, 2006a]. Vaginal oestrogen therapy may be required long-term, as symptoms recur when treatment is stopped. However the endometrial safety of long term or repeated use of topical vaginal oestrogens is uncertain [CSM, 2003b].

- **Systemic hormone replacement therapy (HRT):**

o Combined oestrogen and progestogen cyclical preparations are recommended in perimenopausal women because they produce predictable withdrawal bleeding, whereas continuous regimens often cause unpredictable bleeding [Rees and Purdie, 2006a].

o Treatment for vasomotor symptoms should be continued for at least 1 year; otherwise, symptoms recur. Menopausal symptoms usually resolve within 2–5 years, but some women experience symptoms for many years, even into their seventies and eighties [Rees and Purdie, 2006a].

- **Contraception:**

o Hormone replacement therapy does not suppress ovulation and does not provide contraceptive cover.

- **Hot flushes and night sweats:**

o Good evidence indicates that oral and transdermal HRT with oestrogen alone or oestrogens combined with progestogens is highly effective for reducing the frequency and severity of hot flushes and night sweats caused by the menopause.

- **Vaginal atrophy (dryness and dyspareunia):**

o There is evidence that HRT (combined oral and transdermal [oestrogens and progestogens] or intravaginal oestrogens) is effective for treating vaginal atrophy (dryness, burning and itching, and dyspareunia).

- **Recurrent urinary tract infections:**

o There is evidence that oral and intravaginal oestrogen is effective for preventing urinary tract infections. The appropriate dose and duration of therapy have not been established, and long-term treatment is required because symptoms recur when treatment is stopped [Rees and Purdie, 2006a].

- **Sleep disturbances:**

o By alleviating night sweats, HRT often improves sleep. Women often report improvement in sleep patterns with HRT even if hot flushes or night sweats are not prominent menopausal symptoms [ICSI, 2006]. There is evidence that combined oral oestrogen and progestogen therapy provides a small statistical but not clinically meaningful improvement in sleep disturbances.

- **Incontinence:**

o The British Menopause Society currently recommend the use of oral or topical oestrogen for urinary frequency and urgency [BMS, 2006a]. The evidence to support the use of oestrogens is conflicting. A Cochrane systematic review found evidence that oestrogen treatment improved or cured incontinence; this was more likely with urge incontinence [Moehrer et al, 2003]. However, a subsequently published analysis of the Women's Health Initiative trial found that oestrogen therapy alone and combined with progestogen therapy increased the risk of urinary incontinence among continent women and worsened urinary incontinence among symptomatic women after 1 year [Hendrix et al, 2005].

- **Mood disturbances:**

- No evidence indicates that HRT has a direct effect on mood, irritability, or anxiety. However, HRT may be helpful if other menopausal symptoms, such as hot flushes and sleep disturbances, are present [ICSI, 2006].

- **Libido:**

  - HRT improves urogenital atrophy, thinning, dryness, and loss of elasticity, all of which may cause dyspareunia. While this may improve sexual functioning for many women, HRT has no proven direct benefit on sexuality or libido [ICSI, 2006].
  - There is evidence that loss of libido can be improved by testosterone supplementation, particularly after surgical menopause. Treatment is not always successful, other factors such as marital problems may be involved, and testosterone may cause potentially serious adverse effects [Rees and Purdie, 2006a].
  - Testosterone patches are licensed for women with surgically induced menopause (in women receiving concomitant oestrogen therapy), but they are not recommended for women naturally menopausal or those taking conjugated oestrogens. Safety and efficacy of testosterone patches have not been established beyond 1 year of treatment [BNF 54, 2007].

When should I switch to a continuous combined preparation?

- Consider switching from cyclical therapy to continuous combined therapy when the woman is considered to be postmenopausal. However, it may be difficult to decide when the woman is postmenopausal.
- Women are generally considered to be postmenopausal if:
  - They are more than 54 years of age (it is estimated that 80% of women will be postmenopausal by this age).
  - They have had previous amenorrhoea or increased levels of follicle-stimulating hormone. Women who experienced 6 months of amenorrhoea or had increased follicle-stimulating hormone levels in their mid-40s are likely to be postmenopausal after taking several years of cyclical hormone replacement therapy.

Basis for recommendation

- These recommendations are based on published expert opinion [Rees and Purdie, 2006a].

What follow up is required?

- Review the woman 3 months after starting hormone replacement therapy (HRT) and once each year thereafter.
- At the initial 3-month review:
  - Assess the effectiveness of treatment and adjust to achieve symptom control.
  - See Poor symptom control for more information.
  - Enquire about any adverse effects and manage appropriately.
  - See Managing adverse effects for more information.
  - Enquire about bleeding patterns.
  - Check blood pressure and body weight.
- Once each year:
  - Check effectiveness of treatment and adjust to achieve symptom control.
  - Check for adverse effects and manage appropriately.
  - Consider switching from cyclical HRT to continuous combined HRT, if appropriate.

- Interrupt treatment with intravaginal oestrogen and consider stopping systemic HRT, to re-assess the need for continued use.
- Explain that some of the risks (e.g. breast cancer, ovarian cancer) associated with HRT increase with longer duration of hormone replacement therapy (HRT):
- Breast cancer: combined HRT increases this risk by about 1.6 times after 5 years of use and 2.3 times after 10 years of use. Risk decreases within a few years of stopping HRT.
- Ovarian cancer: long-term use of oestrogen-only HRT and combined HRT may slightly increase the risk. Risk decreases after stopping HRT.
- Perform a breast examination if indicated by personal or family history.
- Encourage breast awareness and participation in the national breast screening programme as appropriate for their age.
- Pelvic examination is required only if clinically indicated (e.g. if there is unscheduled bleeding, especially if heavy, prolonged, or recurrent).
- Check blood pressure.

- Oestrogen levels are rarely indicated.

Clarification / Additional information

- Measurement of estradiol is rarely indicated but may be of use if the clinical response (i.e. symptomatic relief) to HRT is poor [Smellie et al, 2006]:
  - To establish whether absorption of transdermal HRT is adequate in women in whom poor absorption is suspected. If poor absorption is confirmed, prescribe oral HRT.
  - To ensure that oestrogen levels have fallen before implant replacement in women, to avoid supraphysiological concentrations and possible tachyphylaxis.
  - Rarely, in women with persisting symptoms where poor compliance is suspected.

Basis for recommendation

- These recommendations are based on published expert opinion [Working Group on Breast and Pelvic Examination, 2001; RCPE, 2003; AACE Menopause Guidelines Revision Task Force, 2006; Rees and Purdie, 2006a; MHRA and CHM, 2007b; Roberts, 2007].
- An initial review is recommended at 3 months, as most menopausal symptoms respond by then:
  - Vasomotor symptoms: improvement is usually noted within 4 weeks. Usually, hormone replacement therapy (HRT) is used for less than 5 years [BMS, 2006a].
  - Urogenital symptoms: topical oestrogens should be used in the lowest effective amount to minimize systemic absorption [CSM, 2003b]. However long term treatment is often required as symptoms can recur on cessation of therapy [BMS, 2006a]. Treatment should be interrupted as least annually to re-assess the need for continued treatment. If breakthrough bleeding or spotting appears at any time on therapy, the reason should be investigated and may include endometrial biopsy to exclude endometrial malignancy [CSM, 2003b].
- An annual review is recommended because the risks and benefits of HRT for each woman change over time and need to be discussed regularly.
- Blood pressure measurement is not routinely needed, but opportunistic screening is useful.
- **Measurement of follicle-stimulating hormone:**
  - Follicle-stimulating hormone should not be measured because it does not reflect the adequacy of the oestrogen dose and levels may remain increased despite an adequate oestrogen effect [AACE Menopause Guidelines Revision Task Force, 2006].
- **Measurement of oestrogen:**

o This recommendations is based on Best Practice in primary care pathology [Smellie et al, 2006].

When should I refer women who have started HRT?

- Refer women who are taking cyclical hormone replacement therapy if:

o There is a change in pattern of withdrawal bleeds or break through bleeding.

o There is multiple treatment failure e.g. three or more regimens have been tried.

- Refer to a team specializing in the management of gynaecological cancer (depending on local arrangements) any persistent or unexplained bleeding after cessation of hormone therapy for 6 weeks.

Basis for recommendation

- These recommendations are based on published expert opinion [Monga, 2006; Rees and Purdie, 2006b].

- Abnormal bleeding requires investigation if:

o The pattern of withdrawal bleeding or breakthrough bleeding changes while taking monthly cyclical therapy.

o There is breakthrough bleeding that persists for more than 4–6 months or does not lessen while taking a 3-monthly regimen.

How should I manage postmenopausal women with HRT (intact uterus)?

How should I manage post-menopausal women with HRT (intact uterus)?

- Offer lifestyle advice.

- Advise the woman about the risks and benefits of oestrogen-based hormone replacement therapy (HRT) or tibolone as appropriate and record this in her notes.

- Urogenital symptoms alone (e.g. vaginal dryness, dyspareunia, recurrent urinary tract infections, or urinary frequency and urgency):

o Offer treatment with low-dose vaginal oestrogen (cream, pessary, tablet or ring) therapy *or* systemic (oral or transdermal) continuous combined HRT:

o Low-dose vaginal oestrogen may be preferred if the woman does not wish to take systemic HRT or cannot tolerate systemic HRT.

- Vasomotor symptoms (e.g. hot flushes, night sweats), with or without urogenital symptoms:

o Offer systemic (oral or transdermal) continuous combined HRT or tibolone.

- If the woman requires treatment for decreased libido, consider offering tibolone (licensed use).

- For a full discussion on the choice of HRT preparations, see Type of product to offer.

- Give advice regarding contraception:

o A suitable method of contraception should be used for 1 year after the last menstrual period if the woman is more than 50 years of age, or for 2 years after the last menstrual period if the woman is younger than 50 years of age.

o See the CKS topic on Contraception for a detailed discussion on the most appropriate method of contraception in menopausal women and for how long it should be continued.

Clarification / Additional information

- Prescribe hormone replacement therapy at the lowest effective dose for the shortest duration possible.

- Maximal benefit of systemic hormone replacement therapy is usually seen within 3 months, and treatment is generally continued for up to 5 years.

- Urogenital symptoms: topical oestrogens should be used in the lowest effective amount to minimize systemic absorption. Treatment should be interrupted as least annually to re-assess the need for continued treatment. If breakthrough bleeding or spotting appears at any time on therapy, the reason should be investigated and may include endometrial biopsy to exclude endometrial malignancy. Long-term treatment is often required as symptoms can recur on cessation of therapy.

Basis for recommendation

- These recommendations are based on published expert opinion and evidence from systematic reviews and large randomized controlled trials [NZGG, 2004; ICSI, 2006; Rees and Purdie, 2006a; MHRA and CHM, 2007b].

- **Vaginal oestrogens:**

  - Low-dose oestrogen therapy is preferred because it incurs no adverse endometrial effects and a progestogen is not required for endometrial protection [Rees and Purdie, 2006a]. Vaginal oestrogen therapy may be required long-term, as symptoms recur when treatment is stopped. However the endometrial safety of long term or repeated use of topical vaginal oestrogens is uncertain [CSM, 2003b].

- **Continuous combined hormone replacement therapy (HRT):**

  - Cyclical HRT preparations may be used in postmenopausal women; however, continuous combined preparations are generally preferred because they do not induce bleeding.

  - Treatment for vasomotor symptoms should be continued for at least 1 year; otherwise, symptoms recur. Menopausal symptoms usually resolve within 2–5 years, but some women experience symptoms for many years, even into their seventies and eighties [Rees and Purdie, 2006a].

- **Tibolone:**

  - There is evidence that tibolone is effective for treating vasomotor symptoms and improving sexual functioning.

- **Hot flushes and night sweats:**

  - Good evidence indicates that systemic (oral and transdermal) HRT with oestrogen alone or oestrogens combined with progestogens is highly effective for reducing the frequency and severity of hot flushes and night sweats caused by the menopause.

- **Vaginal atrophy (dryness and dyspareunia):**

  - There is evidence that HRT (combined oral oestrogens and progestogens or intravaginal oestrogens) is effective for treating symptoms of vaginal atrophy (dryness, burning and itching, and dyspareunia).

- **Sleep disturbances:**

  - By alleviating night sweats, HRT often improves sleep. Women often report an improvement in sleep patterns with HRT even if hot flushes or night sweats are not prominent menopausal symptoms [ICSI, 2006]. There is evidence that combined oral oestrogen and progestogen therapy provides a small statistical but not clinically meaningful improvement in sleep disturbances.

- **Mood disturbances:**

  - No evidence indicates that HRT has a direct effect on mood, irritability, or anxiety. However HRT may be helpful if other menopausal symptoms, such as hot flushes and sleep disturbances, are present [ICSI, 2006].

- **Libido:**

o HRT improves urogenital atrophy, thinning, dryness, and loss of elasticity, all of which may cause dyspareunia. While this may improve sexual functioning for many women, HRT has no proven direct benefit on sexuality or libido [ICSI, 2006].

o There is evidence that loss of libido can be improved by testosterone supplementation, particularly after surgical menopause. Treatment is not always successful, other factors such as marital problems may be involved, and testosterone may cause potentially serious adverse effects [Rees and Purdie, 2006a].

o Testosterone patches are licensed for women with surgically induced menopause (in women receiving concomitant oestrogen therapy), but they are not recommended for women naturally menopausal or those taking conjugated oestrogens. Safety and efficacy of testosterone patches have not been established beyond 1 year of treatment [BNF 54, 2007].

▪ **Recurrent urinary tract infections:**

o There is evidence that oral and intravaginal oestrogen is effective for preventing urinary tract infections. The appropriate dose and duration of therapy have not been established, and long-term treatment is required because symptoms recur when treatment is stopped [Rees and Purdie, 2006a].

▪ **Incontinence:**

o The British Menopause Society currently recommend the use of oral or topical oestrogen for urinary frequency and urgency [BMS, 2006a]. The evidence to support the use of oestrogens is conflicting. A Cochrane systematic review found evidence that oestrogen treatment improved or cured incontinence; this was more likely with urge incontinence [Moehrer et al, 2003]. However, a subsequently published analysis of the Women's Health Initiative trial found that oestrogen alone or combined with progestogen increased the risk of urinary incontinence among continent women and worsened urinary incontinence among symptomatic women after 1 year [Hendrix et al, 2005].

What follow up is required?

▪ Review the woman 3 months after starting hormone replacement therapy (HRT) and once each year thereafter.

▪ At the initial 3-month review:

o Assess the effectiveness of treatment and adjust to achieve symptom control.

o See Poor symptom control for more information.

o Enquire about any adverse effects and manage appropriately.

o See Managing adverse effects for more information.

o Enquire about bleeding patterns.

o Check blood pressure and body weight.

▪ Once each year:

o Check effectiveness of treatment and adjust to achieve symptom control.

o Check for adverse effects and manage appropriately.

o Consider switching from cyclical HRT to continuous combined HRT, if appropriate.

o Interrupt treatment with intravaginal oestrogen and consider stopping systemic HRT, to re-assess the need for continued use.

o Explain that some of the risks (e.g. breast cancer, ovarian cancer) associated with HRT increase with longer duration of hormone replacement therapy (HRT):

o Breast cancer: combined HRT increases this risk by about 1.6 times after 5 years of use and 2.3 times after 10 years of use. Risk decreases within a few years of stopping HRT.

o Ovarian cancer: long-term use of oestrogen-only HRT and combined HRT may slightly increase the risk. Risk decreases after stopping HRT.

- o Perform a breast examination if indicated by personal or family history.
- o Encourage breast awareness and participation in the national breast screening programme as appropriate for their age.
- o Pelvic examination is required only if clinically indicated (e.g. if there is unscheduled bleeding, especially if heavy, prolonged, or recurrent).
- o Check blood pressure.
- ▪ Oestrogen levels are rarely indicated.

Clarification / Additional information

- ▪ Measurement of estradiol is rarely indicated but may be of use if the clinical response (i.e. symptomatic relief) to HRT is poor [Smellie et al, 2006]:
- o To establish whether absorption of transdermal HRT is adequate in women in whom poor absorption is suspected. If poor absorption is confirmed, prescribe oral HRT.
- o To ensure that oestrogen levels have fallen before implant replacement in women, to avoid supraphysiological concentrations and possible tachyphylaxis.
- o Rarely, in women with persisting symptoms where poor compliance is suspected.

Basis for recommendation

- ▪ These recommendations are based on published expert opinion [Working Group on Breast and Pelvic Examination, 2001; RCPE, 2003; AACE Menopause Guidelines Revision Task Force, 2006; Rees and Purdie, 2006a; MHRA and CHM, 2007b; Roberts, 2007].
- ▪ An initial review is recommended at 3 months, as most menopausal symptoms respond by then:
- o Vasomotor symptoms: improvement is usually noted within 4 weeks. Usually, hormone replacement therapy (HRT) is used for less than 5 years [BMS, 2006a].
- o Urogenital symptoms: topical oestrogens should be used in the lowest effective amount to minimize systemic absorption [CSM, 2003b]. However long term treatment is often required as symptoms can recur on cessation of therapy [BMS, 2006a]. Treatment should be interrupted as least annually to re-assess the need for continued treatment. If breakthrough bleeding or spotting appears at any time on therapy, the reason should be investigated and may include endometrial biopsy to exclude endometrial malignancy [CSM, 2003b].
- ▪ An annual review is recommended because the risks and benefits of HRT for each woman change over time and need to be discussed regularly.
- ▪ Blood pressure measurement is not routinely needed, but opportunistic screening is useful.
- ▪ **Measurement of follicle-stimulating hormone:**
- o Follicle-stimulating hormone should not be measured because it does not reflect the adequacy of the oestrogen dose and levels may remain increased despite an adequate oestrogen effect [AACE Menopause Guidelines Revision Task Force, 2006].
- ▪ **Measurement of oestrogen:**
- o This recommendations is based on Best Practice in primary care pathology [Smellie et al, 2006].

When should I refer women who have started HRT?

- ▪ Refer if:
- o Breakthrough bleeding persists for more than 4–6 months after starting HRT or tibolone.
- o A bleed occurs after amenorrhoea.
- o There is multiple treatment failure e.g. three or more regimens have been tried.

- Refer to a team specializing in the management of gynaecological cancer (depending on local arrangements) any persistent or unexplained bleeding after cessation of hormone therapy for 6 weeks.

Basis for recommendation

- This recommendation is based on pragmatic advice and published expert opinion [Rees and Purdie, 2006b].
- Irregular bleeding or spotting can occur during the first 4–6 months of continuous combined therapy and tibolone and does not require investigation.

How should I manage women who have had a hysterectomy with HRT?

How should I manage women who have had a hysterectomy with HRT?

- Offer lifestyle advice.
- Advise the woman about the risks and benefits of oestrogen-based hormone replacement therapy (HRT) and record this in her notes.
- Urogenital symptoms alone (e.g. vaginal dryness, dyspareunia, recurrent urinary tract infections, or urinary frequency and urgency):
  - Offer treatment with low-dose vaginal oestrogen (cream, pessary, tablet, or ring) *or* systemic (oral or transdermal) oestrogen replacement therapy:
  - Low-dose vaginal oestrogen may be preferred if the woman does not wish to take or cannot tolerate systemic oestrogen.
- Vasomotor symptoms (e.g. hot flushes, night sweats), with or without urogenital symptoms:
  - Offer systemic (oral or transdermal), unopposed oestrogen replacement therapy.
- Decreased libido:
  - Seek specialist advice if considering testosterone patches or implants.
- For a full discussion on the choice of HRT preparations, see Type of product to offer.

Clarification / Additional information

- Urogenital symptoms: long term treatment is often required as symptoms can recur on cessation of therapy.
- Vasomotor symptoms generally respond to systemic therapy within 4 weeks of starting treatment and have a maximal therapeutic effect at 3 months.

Basis for recommendation

- These recommendations are based on published expert opinion and evidence from systematic reviews and large randomized controlled trials [NZGG, 2004; ICSI, 2006; Rees and Purdie, 2006a; MHRA and CHM, 2007b].
- **Oestrogen therapy:**
  - Hysterectomized women should be given oestrogen alone and have no need for progestogen therapy [Rees and Purdie, 2006a]. Progestogens are added to oestrogen therapy to reduce the risk of endometrial hyperplasia and carcinoma which occurs with unopposed oestrogen.

o Treatment for vasomotor symptoms should be continued for at least 1 year; otherwise, symptoms recur. Menopausal symptoms usually resolve within 2–5 years, but some women experience symptoms for many years, even into their seventies and eighties [Rees and Purdie, 2006a].

- **Libido:**

o Hormone replacement therapy (HRT) improves urogenital atrophy, thinning, dryness, and loss of elasticity, all of which may cause dyspareunia. While this may improve sexual functioning for many women, HRT has no proven direct benefit on sexuality or libido [ICSI, 2006].

o There is evidence that loss of libido can be improved by testosterone supplementation, particularly after surgical menopause. Specialist advice should be sought because it is not successful in all women and other factors such as marital problems may be involved [Rees and Purdie, 2006a].

o Testosterone patches are licensed for women with surgically induced menopause (in women receiving concomitant oestrogen therapy), but they are not recommended for women naturally menopausal or those taking conjugated oestrogens. Safety and efficacy of testosterone patches have not been established beyond 1 year of treatment [BNF 54, 2007].

- **Hot flushes and night sweats:**

o Good evidence indicates that systemic HRT with oestrogen alone or oestrogens combined with progestogens is highly effective for reducing the frequency and severity of hot flushes and night sweats caused by the menopause.

- **Vaginal atrophy (dryness and dyspareunia):**

o There is evidence that HRT (combined oral oestrogens and progestogens or intravaginal oestrogens) is effective for treating vaginal atrophy (dryness, burning and itching, and dyspareunia).

- **Recurrent urinary tract infections:**

o There is evidence that oral or intravaginal oestrogen is effective for preventing urinary tract infections. The appropriate dose and duration of therapy have not been established, and long-term treatment is required because symptoms recur when treatment is stopped [Rees and Purdie, 2006a].

- **Sleep disturbances:**

o By alleviating night sweats, HRT often improves sleep. Women often report an improvement in sleep patterns with HRT even if hot flushes or night sweats are not prominent menopausal symptoms [ICSI, 2006]. There is evidence that combined oral oestrogen and progestogen therapy provides a small statistical but not clinically meaningful improvement in sleep disturbances.

- **Incontinence:**

o The British Menopause Society currently recommend the use of oral or topical oestrogen for urinary frequency and urgency [BMS, 2006a]. The evidence to support the use of oestrogens is conflicting. A Cochrane systematic review found evidence that oestrogen treatment improved or cured incontinence; this was more likely with urge incontinence [Moehrer et al, 2003]. However, a subsequently published analysis of the Women's Health Initiative trial found that oestrogen therapy alone and combined with progestogen therapy increased the risk of urinary incontinence among continent women and worsened urinary incontinence among symptomatic women after 1 year [Hendrix et al, 2005].

- **Mood disturbances:**

o No evidence indicates that HRT has a direct effect on mood, irritability, or anxiety. However, HRT may be helpful if other menopausal symptoms, such as hot flushes and sleep disturbances, are present [ICSI, 2006].

Are there any specific issues I should consider in a woman who has had a subtotal hysterectomy?

- A remnant of endometrial tissue may be present in women who have had a subtotal hysterectomy (in which the main part of the uterus is removed but the cervix is retained).

- To test for the presence of endometrial tissue, prescribe a 3-month course of cyclical hormone replacement therapy (HRT):

o If withdrawal bleeding occurs, endometrial tissue is present, and combined HRT should be started:

o For further information on management, see Post-menopausal management with HRT.

o If the woman does not have withdrawal bleeding, endometrial tissue is unlikely to be present, and oestrogen-only HRT may be started:

o For further information on management, see Management with HRT after hysterectomy.

Basis for recommendation

▪ These recommendations are based on published expert opinion [Rees and Purdie, 2006a].

What follow up is required?

▪ Review 3 months after starting hormone replacement therapy (HRT) and once each year thereafter.

▪ At the initial 3-month review:

o Assess the effectiveness of treatment and adjust to achieve symptom control.

o See Poor symptom control for more information.

o Enquire about any adverse effects and manage appropriately.

o See Managing adverse effects for more information.

o Check blood pressure and body weight.

▪ Once each year:

o Check effectiveness of treatment and adjust to achieve symptoms control.

o Check for adverse effects and manage appropriately.

o Re-assess the need for continuing HRT.

o Explain that some of the risks (e.g. ovarian cancer) associated with oestrogen-only HRT increase with longer duration of HRT. The risk decreases after stopping HRT.

o Perform a breast examination if indicated by personal or family history.

o Encourage breast awareness and participation in the national breast screening programme as appropriate for their age.

o Check blood pressure.

▪ Oestrogen levels are rarely indicated.

Clarification / Additional information

▪ Measurement of estradiol is rarely indicated but may be of use if the clinical response (i.e. symptomatic relief) to transdermal HRT is poor [Smellie et al, 2006]:

o To establish whether absorption of transdermal HRT is adequate. If poor absorption is confirmed, prescribe oral HRT.

o To ensure that oestrogen levels have fallen before implant replacement in women, to avoid supraphysiological concentrations and possible tachyphylaxis.

o Rarely, in women with persisting symptoms where poor compliance is suspected.

Basis for recommendation

- These recommendations are based on published expert opinion [Working Group on Breast and Pelvic Examination, 2001; RCPE, 2003; AACE Menopause Guidelines Revision Task Force, 2006; Rees and Purdie, 2006a; MHRA and CHM, 2007b; Roberts, 2007].

- **Review at 3 months:**

o An initial review is recommended at 3 months, as most menopausal symptoms respond by then:

o Vasomotor symptoms: improvement is usually noted within 4 weeks. Usually, hormone replacement therapy (HRT) is used for less than 5 years [BMS, 2006a].

o Urogenital symptoms: vaginal dryness, soreness, superficial dyspareunia, and urinary frequency and urgency respond well to topical or systemic oestrogens. Improvement may take several months, and symptoms may recur if treatment is stopped. Long-term treatment is often required [BMS, 2006a].

- **Annual review:**

o An annual review is recommended because the risks and benefits of HRT for each woman change over time and need to be discussed regularly.

o Blood pressure measurement is not routinely needed, but opportunistic screening is useful.

- **Measurement of follicle-stimulating hormone:**

o Follicle-stimulating hormone should not be measured because it does not reflect the adequacy of the oestrogen dose and levels may remain increased despite an adequate oestrogen effect [AACE Menopause Guidelines Revision Task Force, 2006].

- **Measurement of oestrogen:**

o This recommendations is based on Best Practice in primary care pathology [Smellie et al, 2006].

When should I refer women who have started HRT?

- Refer to secondary care if there is multiple treatment failure e.g. three or more regimens have been tried.

Basis for recommendation

- This recommendation is based on pragmatic advice and published expert opinion [Rees and Purdie, 2006b].

What should I do if there is poor symptom control?

- Review the woman:

o Check that the hormone replacement therapy (HRT) has been used as recommended for at least 3 months to ensure full effect.

o Check that patches are adherent.

o Review the woman's expectations. Hormone replacement therapy can help symptoms due to oestrogen deficiency but is not an answer to all problems.

o Consider an alternative diagnosis. See Other causes of the symptoms.

- Treatment options include:

o Increasing the oestrogen dose.

o Adding vaginal oestrogen if urogenital symptoms are not controlled.

o Switching from oral to a non-oral route (e.g. if absorption is poor because of a bowel disorder or if a drug interaction is present).

- Switching delivery system if patch adhesion is poor.

Basis for recommendation

- These recommendations are based on expert published opinion and pragmatic advice [Rees and Purdie, 2006a; Menopause Matters, 2007b].

When should I consider stopping HRT?

- If systemic HRT is being used for symptom control consider a trial withdrawal (if a woman is symptom-free) after 1–2 years of hormone replacement therapy (HRT).
  - Advise the woman that symptoms may recur for a short time once HRT is stopped.
  - Counsel the woman about the possible risks of HRT if she wishes to continue treatment, particularly if treatment is being used for longer than 5 years.
- Topical (vaginal) oestrogen may be required long term as symptoms can recur once treatment has stopped.
  - Stop treatment at least annually to re-assess the need for continued treatment.
- Women with premature menopause usually take hormone replacement therapy up to the age of the natural menopause (50 years); at that time, therapy is reassessed. Some women will still be symptomatic.

Basis for recommendation

- These recommendations are based on pragmatic advice and published expert opinion [RCPE, 2003; Rees and Purdie, 2006a].
- Vasomotor symptoms usually resolve within 2–5 years, but some women experience symptoms for many years.
- **Topical oestrogens:**
  - Endometrial effects should not be incurred with low dose oestrogens such as vaginal estriol (cream or pessary) or estradiol (tablet or ring). A progestogen is not needed with such low dose preparations [Rees and Purdie, 2006a].
  - The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain. The Medicines and Healthcare products Regulatory Agency (MHRA) have advised that treatment with topical oestrogens should be interrupted at least annually to re-assess the need for continued treatment [CSM, 2003b].

How should I manage women with a premature menopause?

How can I manage women with a premature menopause?

- Offer lifestyle advice.
- Refer women who are younger than 40 years of age to a gynaecologist.
- Offer systemic oestrogen replacement therapy.
  - Systemic hormone replacement therapy (HRT) or the combined oral contraceptive pill (COC) may be used.
- **HRT:** the HRT regimens used will depend on whether or not the woman has undergone a hysterectomy, still has some ovarian activity, and still has periods.
  - For women who are still having periods, offer combined, systemic (oral or transdermal), cyclical HRT:
  - For women with infrequent periods or who cannot tolerate progestogens, a systemic 3-monthly regimen may be preferred.

o For women who have had a hysterectomy, offer oral or transdermal unopposed oestrogen replacement therapy.

- **COC:** whether or not the woman can be prescribed the COC will depend upon the woman's age and associated risk factors (e.g. smoking).

- Advise the woman that she may still become pregnant if contraception is not used.

o See the CKS topic on Contraception for a detailed discussion on the use of contraception in perimenopausal women.

- Testosterone implants and patches (licensed) may be considered for treating decreased libido (especially in oophorectomized women); however, seek specialist advice before prescribing.

Clarification / Additional information

- For the purposes of this guideline, premature menopause is menopause which occurs in women less than 45 years of age.

- After 50 years of age, therapy for osteoporosis should be reassessed.

Basis for recommendation

- These recommendations are based on published expert opinion [CSM, 2003a; Rees and Purdie, 2006a; SOGC, 2006].

- Feedback from expert reviewers recommend that women less than 40 years of age should be referred for investigation to determine the cause of premature menopause (e.g. primary ovarian failure) and to discuss fertility if appropriate. Women who have primary ovarian failure may continue to ovulate infrequently and require advice on appropriate contraception.

- **Hormone replacement therapy (HRT):**

o Women who have premature menopause require treatment to prevent osteoporosis and to treat menopausal symptoms. There is evidence that HRT reduces the risk of spine and hip fracture, as well as other osteoporotic fractures [Writing Group for the Women's Health Initiative Investigators, 2002; Women's Health Initiative, 2004].

- **The combined oral contraceptive (COC) containing oestrogen and progestogen:**

o The COC is often prescribed for younger women because it does not have the stigma of old age that HRT may have. However, trial evidence is scant on which to recommend treatment with a COC [Rees and Purdie, 2006a; SOGC, 2006]. The COC is perhaps more useful when contraception is still thought to be required (e.g. ovulation can occur for several years after premature ovarian failure in some women).

o The dose of ethinylestradiol used in standard pills is sufficient to provide control of menopausal symptoms and osteoporosis prophylaxis; however, oral contraceptives provide oestrogen for only 3 weeks in every 4 (the fourth week being pill-free). For women who are oestrogen deficient, the lack of oestrogen during this pill-free week can cause symptoms, and it may be more appropriate to provide oestrogen continuously, as with most forms of HRT.

- **Testosterone:**

o There is evidence that loss of libido can be improved by testosterone supplementation particularly after surgical menopause. Treatment is not always successful, other factors such as marital problems may be involved, and and testosterone may cause potentially serious adverse effects [Rees and Purdie, 2006a].

What follow-up is required?

- Review 3 months after starting hormone replacement therapy (HRT) and once each year thereafter.

- At the initial 3-month review:

- Assess the effectiveness of treatment and adjust to achieve symptom control.
- See Poor symptom control for more information.
- Enquire about any adverse effects and manage appropriately.
- See Managing adverse effects for more information.
- Check blood pressure and body weight.

▪ Once each year:

- Check effectiveness of treatment and adjust to achieve symptoms control.
- Check for adverse effects and manage appropriately.
- Interrupt treatment with intravaginal oestrogen to re-assess the need for continued use.
- Re-assess the need for continuing systemic HRT.
- Explain that some of the risks (e.g. ovarian cancer) associated with oestrogen-only HRT increase with longer duration of HRT. The risk decreases after stopping HRT.
- Perform a breast examination if indicated by personal or family history.
- Encourage breast awareness and participation in the national breast screening programme as appropriate for their age.
- Pelvic examination is required only if clinically indicated (e.g. if there is unscheduled bleeding, especially if heavy, prolonged, or recurrent).
- Check blood pressure.

▪ Oestrogen levels are rarely indicated.

Clarification / Additional information

▪ Measurement of estradiol is rarely indicated but may be of use if the clinical response (i.e. symptomatic relief) to transdermal HRT is poor [Smellie et al, 2006]:

- To establish whether absorption of transdermal HRT is adequate. If poor absorption is confirmed, prescribe oral HRT.
- To ensure that oestrogen levels have fallen before implant replacement in women, to avoid supraphysiological concentrations and possible tachyphylaxis.
- Rarely, in women with persisting symptoms where poor compliance is suspected.

Basis for recommendation

▪ These recommendations are based on published expert opinion [Working Group on Breast and Pelvic Examination, 2001; RCPE, 2003; AACE Menopause Guidelines Revision Task Force, 2006; Rees and Purdie, 2006a; MHRA and CHM, 2007b; Roberts, 2007].

▪ **Review at 3 months:**

- An initial review is recommended at 3 months, as most menopausal symptoms respond by then:
- Vasomotor symptoms: improvement is usually noted within 4 weeks. Usually, hormone replacement therapy (HRT) is used for less than 5 years [BMS, 2006a].
- Urogenital symptoms: vaginal dryness, soreness, superficial dyspareunia, and urinary frequency and urgency respond well to topical or systemic oestrogens. Improvement may take several months, and symptoms may recur if treatment is stopped. Long-term treatment is often required [BMS, 2006a].

▪ **Annual review:**

- An annual review is recommended because the risks and benefits of HRT for each woman change over time and need to be discussed regularly.
- Blood pressure measurement is not routinely needed, but opportunistic screening is useful.

- **Measurement of follicle-stimulating hormone:**
  - Follicle-stimulating hormone should not be measured because it does not reflect the adequacy of the oestrogen dose and levels may remain increased despite an adequate oestrogen effect [AACE Menopause Guidelines Revision Task Force, 2006].
- **Measurement of oestrogen:**
  - This recommendations is based on Best Practice in primary care pathology [Smellie et al, 2006].

When should I refer a women with premature menopause who has started HRT?

- For women taking cyclical hormone replacement therapy refer if:
  - There is a change in pattern of withdrawal bleeds or breakthrough bleeding.
- For women taking continuous combined HRT or long cycle regimens refer if:
  - Breakthrough bleeding persists for more than 4–6 months after starting therapy.
  - A bleed occurs after amenorrhoea.
- Refer if there is multiple treatment failure e.g. three or more regimens have been tried.
- Refer to a team specializing in the management of gynaecological cancer (depending on local arrangements) any persistent or unexplained bleeding after cessation of hormone therapy for 6 weeks.

Basis for recommendation

- This recommendation is based on pragmatic advice and published expert opinion [Rees and Purdie, 2006b].

How can I manage menopausal symptoms without HRT?

How can I manage menopausal symptoms without HRT?

- Offer lifestyle advice to control symptoms; if this is not effective, consider other treatments.
- For vasomotor symptoms, consider:
  - A trial (2 weeks) of paroxetine (20 mg daily), fluoxetine (20 mg daily), citalopram (20 mg daily), or venlafaxine 37.5 mg twice a day.
  - Antidepressants are unlicensed for treating menopausal symptoms.
  - A trial (2–4 weeks) of clonidine (50 to 75 micrograms twice a day, licensed use).
  - Seek specialist advice if a progestogen such as norethisterone or megestrol (both unlicensed) are being considered.
- For vaginal dryness, prescribe a vaginal lubricant or moisturizer, such as Replens MD®.
- Manage psychological symptoms, such as mood disturbances, anxiety, and depression, on an individual basis. They may be addressed using self-help groups, psychotherapy, other forms of counselling, or antidepressants.
- CKS does not recommend the use of complementary therapies (e.g. soy, red clover, black cohosh). If complementary or herbal products are being used, advise the woman that:
  - The efficacy of these products has not yet been established.

- o There is very little control over the quality of the products available, which may vary considerably.
- o Some of these treatments (ginseng, black cohosh, and red clover) have oestrogenic properties and should not be used in women with contraindications to oestrogen (e.g. breast cancer).
- o Long-term safety (e.g. effects on the breast and endometrium) have not been assessed.
- o Some treatments may have serious adverse effects (e.g. liver toxicity has been reported with black cohosh and kava):
- o Kava has been withdrawn from the UK market.
- o Dong quai extracts and some species of red clover contain coumarins, which make them unsuitable for women taking anticoagulants.

Basis for recommendation

- ▪ These recommendations are based on published expert opinion from the Medicines and Healthcare products Regulatory Agency, formerly known as the Committee on Safety of Medicines [CSM, 2003; CSM, 2004; ICSI, 2006; RCOG, 2006; Rees and Purdie, 2006].
- ▪ **Progestogens:**
- o There is evidence that norethisterone and megestrol are effective for treating hot flushes. However, doses which achieve vasomotor control may increase the risk of thromboembolism and may not be suitable for women at increased risk of thromboembolic disease (personal or family history, known thrombophilia) [BMS, 2006]. Long term safety data is lacking.
- ▪ **Antidepressants:**
- o Limited evidence indicates that venlafaxine, fluoxetine, citalopram, and paroxetine are effective for treating hot flushes. They are not licensed for this use but may be considered in treating women who cannot, or do not want to take hormone replacement therapy.
- o When effective, antidepressants provide relief from hot flushes almost immediately. A 1-week trial is generally sufficient to determine whether an antidepressant is going to be effective [ICSI, 2006].
- ▪ **Clonidine:**
- o Clonidine is licensed for the treatment of vasomotor symptoms. There is limited evidence of its efficacy. It may cause unacceptable adverse effects (e.g. dry mouth, sedation, depression, fluid retention) [Rees and Purdie, 2006; BNF 54, 2007].
- o Clonidine should be stopped if no benefit is noted after 2–4 weeks of treatment or if a woman experiences adverse effects, including dizziness, dry mouth, drowsiness, and constipation [SOGC, 2006].
- ▪ **Complementary therapies:**
- o No convincing evidence indicates that complementary therapies are effective for managing menopausal symptoms, but prospective randomized controlled trials are required to confirm the efficacy and long-term safety of these therapies [RCOG, 2006].
- ▪ **Other treatments:**
- o Gabapentin:
- o Limited evidence indicates that gabapentin is effective for reducing hot flushes; further work is being done to confirm this, and use of gabapentin is restricted to specialist centres [RCOG, 2006].
- o Beta-blockers:
- o Beta-blockers should not be used to treat menopausal symptoms because effectiveness has not been established [RCOG, 2006; Rees and Purdie, 2006].

What follow up is required?

- Advise the woman to return if:
    - Lifestyle measures alone have been of insufficient benefit or her symptoms worsen.
    - She does not respond to antidepressant treatment within 2 weeks.
    - Clonidine was started and her symptoms have not improved in 4 weeks, or she is experiencing adverse effects, such as dizziness or constipation.
- Review all women at least annually.

Basis for recommendation

- There is no published guidance on when to follow up menopausal women who are being treated with alternatives to hormone replacement therapy. These recommendations are based on pragmatic advice.
- Women who are going to respond to antidepressants generally do so within 1–2 weeks.
- Women who start clonidine therapy usually respond to treatment within 2–4 weeks.

When should I consider stopping treatment?

- Consider stopping treatment if a woman is symptom-free on treatment; a trial withdrawal can be undertaken after 1–2 years of therapy.
- Advise that symptoms sometimes recur once treatment is stopped.
- Use of vaginal moisturizers and lubricants may be continued indefinitely.

Basis for recommendation

- There is no published guidance on the duration of therapy for alternatives to hormone replacement therapy.
- Vasomotor symptoms usually resolve within 2–5 years [Rees and Purdie, 2006a].

How should I manage women with a comorbidity?

How should I manage a woman with current or previous endometrial cancer?

- Offer lifestyle advice or non-HRT therapies initially.
- If these are inadequate and the woman requires treatment, seek specialist advice from an oncologist or a specialist menopause clinic for the most appropriate treatment.

Clarification / Additional information

- Management usually depends on the stage of the cancer. Treatment with hormone replacement therapy is usually limited to women with stage I disease, although women with stage II disease are occasionally treated.
- In stage I endometrial cancer, specialists may advise that oestrogens can sometimes be used. Progestogens (in opposition to oestrogen or alone) may also be used.

Basis for recommendation

- This recommendation is based on published expert opinion [Mueck and Seeger, 2003; SOGC, 2006].

How should I manage a woman with a personal or family history of thromboembolic disease or with a known thrombophilia disorder?

- Offer lifestyle advice or manage menopausal symptoms without HRT initially.
- Refer to a specialist in thrombophilia if these measures are inadequate and the woman requires treatment.

Basis for recommendation

- These recommendations are based on published expert opinion [RCOG, 2004; ICSI, 2006].
- **Women with a personal or family history of thromboembolic disease** should avoid using oral hormone replacement therapy (HRT) (in view of the relatively high risk of recurrent venous thromboembolism [VTE]) unless it is taken with anticoagulation therapy:
  - Transdermal therapy may be a better option, but specialist advice should be sought.
  - Evidence indicates that oral HRT and not transdermal HRT is associated with an increased risk of VTE.
  - Transdermal therapy is thought to have less effect on coagulation than oral administration because oral preparations undergo first-pass hepatic metabolism and therefore have a greater effect on factors produced by the liver than transdermal preparations, which avoid the first-pass effect.
- **Women with a known thrombophilia disorder:**
  - In general, women with antithrombin defects, or combinations of other clotting defects, and Factor V Leiden homozygosity should avoid HRT, unless it is taken with anticoagulation therapy (these women should be managed via specialist centres).
  - Evidence is insufficient to recommend that women with other clotting defects completely avoid HRT. However, HRT should be avoided in the presence of multiple risk factors for VTE in these women (e.g. varicose veins, obesity).

How should I manage a woman with current or previous breast cancer?

- Offer lifestyle advice or non-HRT therapies initially.
- If a woman with a significant family history of breast cancer requires hormone replacement therapy (HRT), refer to a specialist breast clinic to determine her personal risk, without which an informed decision cannot be made.
- For women with current or previous breast cancer who have severe menopausal symptoms, seek specialist advice from the local oncologist or specialist menopausal clinic.

Basis for recommendation

- This recommendation is based on published expert opinion [Rees and Purdie, 2006a].
- Hormone replacement therapy remains contraindicated in women who have had breast cancer.
- Troublesome symptoms of oestrogen deficiency are common in women receiving treatment for breast cancer. Hormone replacement therapy has been given with tamoxifen but should be avoided in women taking aromatase inhibitors (e.g. anastrozole) [RCPE, 2003].

Important aspects of prescribing information relevant to primary healthcare are covered in this section specifically for the drugs recommended in this CKS topic. For further information on contraindications, cautions, drug interactions, and adverse effects, see the electronic Medicines Compendium (eMC) (http://emc.medicines.org.uk), or the British National Formulary (BNF) (www.bnf.org).

Hormone replacement therapy (HRT)

What types of HRT are available?

- Oestrogen-only preparations include:
    - Oral tablet (daily).
    - Transdermal patch (once weekly or twice weekly) or gel (daily).
    - Vaginal ring (Estring®), creams and pessaries.
    - Implant (every 6 months).
- Combined oestrogen–progestogen preparations include:
    - Oral tablet (daily).
    - Transdermal patch (once weekly or twice weekly):
    - In transdermal combined hormone replacement therapy (cyclical or continuous combined oestrogen plus progestogen), the progestogen is either combined into the patch, or given separately as a tablet.

[BNF 54, 2007]

Which type of HRT product should I offer?

Which hormone should I use?

- **Choice of systemic oestrogen:**
    - 'Natural' oestrogens, such as conjugated oestrogen, estradiol, estrone, and estriol, are suitable for use as systemic hormone replacement therapy (HRT).
- **Choice of vaginal oestrogen:**
    - Low dose oestrogens such as estriol (cream or pessary) or estradiol (tablet or ring) preparations are suitable for topical (vaginal) use. Endometrial effects should not be incurred. A progestogen is not needed with such low dose preparations [Rees and Purdie, 2006a].
    - Synthetic or conjugated oestrogens should be avoided as they are well absorbed from the vagina and may potentially result in endometrial stimulation.
- **Choice of progestogen:**
    - The progestogens most commonly used in HRT are almost all synthetic and include:
    - Dydrogesterone and medroxyprogesterone.
    - Norethisterone and levonorgestrel.
    - Drospirenone.
    - Women vary in their tolerance to progestogens.
    - Medroxyprogesterone and dydrogesterone are sometimes better tolerated than norethisterone or levonorgestrel because they are less androgenic.
    - Drospirenone is also considered to be less androgenic and has aldosterone antagonistic activities. It is useful for women who complain of fluid retention during the progestogen phase.

o Combined HRT tablets contain medroxyprogesterone, dydrogesterone, or drospirenone (less androgenic); or norethisterone, or levonorgestrel (more androgenic).

o Combined HRT patches only contain norethisterone or levonorgestrel (more androgenic). There are currently no patches containing less androgenic progestogens.

o The levonorgestrel-releasing intrauterine system is an alternative route of delivery of progestogen to protect the endometrium. Since levonorgestrel is delivered locally to the uterus, a much lower daily dose is used, which also results in low systemic levels of levonorgestrel.

▪ **Tibolone** is a synthetic steroidal agent with oestrogenic, progestogenic, and androgenic activity. It may be used as an alternative to combined therapy for postmenopausal women who wish to have amenorrhoea.

▪ **Testosterone supplementation** (patches and implants) can improve loss of libido, particularly after surgical menopause. Treatment is not always successful, other factors such as marital problems may be involved, and testosterone may cause potentially serious adverse effects [Rees and Purdie, 2006a].

o Testosterone patches are licensed for women with surgically induced menopause (in women receiving concomitant oestrogen therapy), but they are not recommended for women naturally menopausal or those taking conjugated oestrogens. Safety and efficacy of testosterone patches have not been established beyond 1 year of treatment [BNF 54, 2007].

Clarification / Additional information

▪ For the purposes of this guideline, 'natural oestrogen' is defined as one that is found in normal physiology, irrespective of whether it has been prepared by chemical synthesis or extraction from a plant or animal source.

Basis for recommendation

▪ These recommendations are based on published expert opinion [Rees and Purdie, 2006a].

▪ Synthetic oestrogens, such as mestranol or ethinylestradiol, are generally considered not to be suitable for hormone replacement therapy (except in women with early ovarian failure) because of their greater metabolic impact.

Which regimen should I use?

▪ Offer oestrogen-only hormone replacement therapy (HRT) for women who do not have a uterus (usually taken continuously).

▪ Offer combined (oestrogen and progestogen) HRT to women with an intact uterus:

o For perimenopausal women, monthly or 3-monthly cyclical regimens may be used:

o A 3-monthly regimen may be more suitable for women with infrequent periods or who are intolerant of progestogens.

o A monthly regimen produces monthly bleeding and a 3-monthly regimen produces a bleed every three months.

o For postmenopausal women, monthly, 3-monthly cyclical regimens, or continuous combined regimens may be used. Continuous combined regimens may be preferred because they do not produce withdrawal bleeding:

o Continuous combined HRT may produce irregular bleeding or spotting the first 4–6 months of treatment. Bleeding should be investigated if it persists beyond 6 months, if it becomes heavier rather than less, or it if occurs after amenorrhoea.

▪ Tibolone is an alternative no-bleed regimen for postmenopausal women.

- It is preferable for the oestrogen and progestogen to be in combined form (e.g. in one tablet), because the adverse effects of the progestogen may lead to poor compliance if given separately. If oestrogen and progestogen are given separately, an explanation about the endometrial protective effect of progestogens is important to ensure compliance.

Clarification / Additional information

- Combined hormone replacement therapy regimens:

o Monthly cyclical regimens: oestrogen is taken daily and progestogen given at the end of the cycle for 10–14 days.

o Three-monthly cyclical regimens: oestrogen is taken every day and progestogen is given for 14 days every 13 weeks.

o Continuous combined regimens: oestrogen and progestogen are taken every day.

Basis for recommendation

- These recommendations are based on expert published opinion [Rees and Purdie, 2006a].

- **Hysterectomy:**

o Women who have a had a hysterectomy do not usually require the addition of progestogen. Progestogens are added to hormone replacement therapy regimens to reduce the increased risk of endometrial hyperplasia and cancer which occurs with unopposed oestrogen.

- **Perimenopausal women:**

o Continuous regimens are not recommended because they often cause unpredictable bleeding in these women.

Which route should I use?

- **Oral or transdermal preparations** may be used to treat urogenital symptoms or vasomotor symptoms (e.g. flushes or sweats) with or without urogenital symptoms.

o Transdermal preparations may be appropriate if:

o The woman prefers this route.

o Symptom control is poor with oral treatment.

o Oral treatment causes adverse effects (e.g. nausea).

o History of or risk of venous thromboembolism (in this situation, consider hormone replacement therapy [HRT] only after full discussion and appropriate investigation).

o The woman is taking a hepatic enzyme–inducing drug (e.g. anticonvulsant therapy).

o The woman has a bowel disorder which may affect absorption of oral therapy.

o The woman has a history of migraine (when steadier hormone levels may be beneficial).

o The woman has lactose sensitivity (most HRT tablets contain lactose).

- **Low-dose vaginal oestrogen** (tablet, cream, pessary, or vaginal ring) may be used for urogenital symptoms alone.

- **Offer the levonorgestrel-releasing intrauterine system (Mirena®)** when:

o The woman is experiencing persistent progestogenic adverse effects from systemic HRT despite changes in type and route of progestogen.

o Contraception is required along with HRT in the perimenopause.

- Withdrawal bleeds on sequential HRT are heavy, after investigation if indicated.

- **Estradiol implants** are usually offered as a last resort in women post-hysterectomy when symptoms are not controlled by other means. Implants release estradiol over many months (replaced every 6 months) so that the woman does not have to remember to take medication. However, they can scar the skin and cannot be easily removed.

Basis for recommendation

- These recommendations are based on pragmatic advice and published expert opinion [Rees and Purdie, 2006a].
- Oral oestrogens are more likely to cause nausea than other forms of oestrogen.
- **Vaginal oestrogen:**
    - Systemic absorption of low-dose vaginal oestrogen is very low and does not relieve other menopausal symptoms, such as hot flushes.
- **Patches:**
    - Hormone levels delivered by patch are more constant than if given orally; oestrogen is absorbed directly through the skin into the systemic circulation, bypassing the liver.
    - Some patches come in four strengths of oestrogen, allowing titration to the optimal dose.
- **Mirena®:**
    - Mirena® provides adequate endometrial protection. The oestrogen dose and route can be tailored to meet individual needs.
    - Progestogenic systemic absorption is minimal, reducing systemic progestogenic side effects. The endometrial effect of Mirena® can significantly reduce bleeding when used as part of a hormone replacement therapy regimen: 30–60% of women become amenorrhoeic. Although Mirena used for contraception is licensed for 5 years, the license for use for the progestogen part of hormone replacement therapy is currently 4 years.
- **Estradiol implants:**
    - Recurrence of vasomotor symptoms at supraphysiological plasma concentrations may occur. Moreover, there is evidence of prolonged endometrial stimulation after discontinuation (calling for continuous cyclical progestogen) [BNF 54, 2007].

Which dose should I use?

- The lowest effective dose of hormone replacement therapy should be used for the shortest time possible.
- **Oestrogen dose for symptom control:**
    - Older women may be less tolerant of oestrogen and need to start (and are usually maintained) on a lower dose (e.g. oral estradiol 1 mg, or transdermal estradiol 25–50 micrograms). Younger women may require higher doses (e.g. 2–4 mg estradiol, or transdermal estradiol 100 micrograms) to remain symptom-free. The dose should be tailored to the symptoms since the ingested or applied dose may not be well absorbed.
- **Oestrogen dose for osteoporosis:**
    - The 'standard' bone-conserving doses of oestrogen are considered to be estradiol 2 mg, conjugated equine oestrogens 0.625 mg, or transdermal 50 microgram patch. However, it is now evident that lower doses also conserve bone mass.
- **Progestogens for endometrial protection:** several different progestogens used in combined hormone replacement therapy provide adequate endometrial protection. See Table 1 for more information.

- **Tibolone:** the standard dose is 2.5 mg daily.

Clarification / Additional information

Table 1. Accepted doses of progestogen for endometrial protection.

Progestogen type and route	Accepted endometrial protection dosage
clical preparations	
Norethisterone oral	1 mg for last 12–14 days of 28-day cycle
Norethisterone patc	170–250 micrograms for last 14 days of a 28-c cycle
Levonorgestrel oral	75–250 micrograms for last 12 days of 28-day
Levonorgestrel patc	10 micrograms for last 14 days of 28-day cycle
Norgestrel oral	150–500 micrograms for last 12 days of 28-day cycle
Medroxyprogesterone acetate oral	10 mg for last 14 days of 28-day cycle 20 mg for last 14 days of 3-month cycle
Dydrogesterone ora	10–20 mg for last 14 days of 28-day cycle
Continuous regimens	
Norethisterone oral	0.5–1 mg
Norethisterone patc	170 micrograms
Levonorgestrel patc	7 micrograms
Medroxyprogesterone acetate oral	2.5–5 mg
Dydrogesterone	5 mg

Data from: [BNF 54, 2007]

Basis for recommendation

- These recommendations are based on published expert opinion [Rees and Purdie, 2006a; MHRA and CHM, 2007b].

How do I manage the adverse effects of HRT?

How do I manage weight gain?

- Reassure the woman that weight gain is very common around the time of the menopause and that hormone replacement therapy does not cause significant further weight gain.

Basis for recommendation

- These recommendations are based on published expert opinion [Kongnyuy et al, 1999; Rees and Purdie, 2006a].

- Weight gain is often cited as a major reason why women are reluctant to start or continue hormone replacement therapy.

How do I manage oestrogen-related adverse effects?

- **Oestrogen-related adverse effects** include fluid retention, bloating, breast tenderness or enlargement, nausea, headaches, leg cramps, and dyspepsia. They may occur continuously or randomly throughout the cycle.

- **Encourage the woman to persist with therapy for about 3 months** to await resolution, as most adverse effects resolve with increased duration of use:

  - **Leg cramps** can improve with lifestyle changes, including exercise and regular stretching of the calf muscles.

  - **Nausea/gastric upset** may be helped by adjusting the timing of the oestrogen dosage or taking with food.

  - **Breast tenderness** may be alleviated by a low-fat, high-carbohydrate diet. Gamolenic acid (evening primrose oil) is no longer available as a licensed medicinal product because of lack of efficacy.

  - **Migraine** triggered by fluctuating oestrogen levels may respond to transdermal therapy, as this produces more stable oestrogen levels.

- **For persistent adverse effects, consider:**

  - **Reducing the dosage** *or*

  - **Changing the oestrogen type** (e.g. swap between the two main forms of oestrogen, that is, estradiol and conjugated oestrogens) *or*

  - **Changing the route** of delivery (e.g. tablets may cause nausea, but patches and gels generally do not).

Basis for recommendation

- These recommendations are based on published expert opinion [Bundred, 2003; Rees and Purdie, 2006a; Menopause Matters, 2007a].

- The recommended management strategies have not been assessed in clinical trials.

How do I manage progestogen-related adverse effects (other than bleeding)?

- Progestogen-related adverse effects tend to occur in a cyclical pattern during the progestogen phase of cyclical hormone replacement therapy (HRT). They include fluid retention, breast tenderness, headaches or migraine, mood swings, depression, acne, lower abdominal pain, and backache.

- Encourage the woman to persist with therapy for about 3 months to await possible resolution of adverse effects.

- For persistent or troublesome symptoms, consider the following options. Many of these are the opposite of what may be needed to better control bleeding:

  - **Changing the progestogen type,** for example from more androgenic ones, such as norethisterone and norgestrel, to less androgenic ones, such as medroxyprogesterone or dydrogesterone.

  - **Changing the route of progestogen,** for example from oral to transdermal, vaginal, or intrauterine progestogen. This may be most beneficial when the woman is nauseous while receiving oral HRT. If the oestrogen is to be delivered by a different route to the progestogen, the woman can easily miss out the progestogen as desired if it is causing unpleasant adverse effects. However, the woman must fully understand that the progestogen is being given to provide endometrial protection.

- **Reducing the duration of progestogen administration:** progestogens can be taken for 12–14 days of each monthly sequential regimen, so swapping from a 14-day to a 12-day product may provide benefit.
- **Changing to a product with a lower dose of progestogen** (dosages are preparation dependent).
- **Reducing the frequency** of progestogen dosing. This can be achieved by switching to a long-cycle regimen administering progestogen for 14 days every 3 months (but this strategy is suitable only for women without natural regular periods).
- **Changing to continuous combined therapy** or tibolone often reduces progestogenic adverse effects with established use (as these products contain lower dosages of progestogen), but this is suitable only for postmenopausal women.

Basis for recommendation

- These recommendations are based on published expert opinion [Rees and Purdie, 2006a; Menopause Matters, 2007a].

How do I manage bleeding on monthly cyclical regimens?

- Examine the woman, visualize the cervix and check smears are up to date, and refer for transvaginal ultrasound to exclude pelvic abnormalities before changing treatment.
- Check for compliance with therapy, drug interactions (e.g. anticonvulsants), or gastrointestinal upset.
- **Altering the progestogen part of the regimen may improve bleeding:**
  - **Heavy or prolonged bleeding:** increase the duration or dosage of the progestogen, or change the type of progestogen. Idiopathic menorrhagia may be helped by using the levonorgestrel-releasing intrauterine system combined with an oestrogen delivered orally or transdermally.
  - **Bleeding early in the progestogen phase:** increase dosage or change the type of progestogen.
  - **Irregular bleeding:** change regimen or increase the dosage of progestogen.
  - **No bleeding whilst taking a cyclical regimen** reflects an atrophic endometrium and occurs in 5% of women. Pregnancy needs to be excluded in perimenopausal women. Check compliance if the progestogen component is taken separately.

Clarification / Additional information

- It is mandatory to investigate before changing treatment because pelvic pathology can be missed. Changing treatment before examination is unsafe practice and can lead to delayed diagnosis of endometrial cancer.

Basis for recommendation

- These recommendations are based on published expert opinion [Rees and Purdie, 2006a; Menopause Matters, 2007a].
- Monthly cyclical regimens should produce regular predictable bleeding starting towards or soon after the end of the progestogen phase. Unpredictable or unacceptable bleeding may be due to non-adherence to therapy, drug interactions, or gastrointestinal upset (or cancer, if not already excluded).

How do I manage bleeding on continuous combined or during long cycle HRT regimens?

- Irregular breakthrough bleeding or spotting is common in the first 3–6 months of therapy, but bleeding beyond 6 months or after a spell of amenorrhoea requires further investigation or referral.

Basis for recommendation

- These recommendations are based on published expert opinion [Rees and Purdie, 2006a; Menopause Matters, 2007a].

What are the contraindications to HRT?

- Contraindications to HRT are:
  - Hormone-dependent cancer (e.g. endometrial cancer, current or past breast cancer).
  - Active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction).
  - Venous thromboembolic disease, pulmonary embolism, or current pregnancy.
  - Severe active liver disease.
  - Undiagnosed breast mass.
  - Uninvestigated abnormal vaginal bleeding.

How should HRT be stopped?

- Some women do not notice any symptoms even with abrupt cessation of hormone replacement therapy (HRT), while others may experience a recurrence of hot flushes and sweats.
- Some experts suggest that HRT should be gradually reduced rather than stopped abruptly. Suggested strategies are:
  - **Oestrogen-only tablets:** reduce from a 2 mg to a 1 mg tablet for 1–2 months, then use 1 mg on alternate days for a further 1–2 months.
  - **Oestrogen-only patches:** reduce the dose gradually to 25 micrograms daily (e.g. step the dose down a patch strength each month). Half a matrix-type patch (12.5 micrograms daily) can be used for a further 1–2 months.
  - **Cyclical combined HRT tablets:** reduce to a cyclical HRT pack containing 1 mg estradiol for 1–2 months. Cut the tablet in half for the next 1–2 months; this will ensure that the woman still receives oestrogen combined with a progestogen.
  - **Cyclical combined HRT patches:** reduce the dose as for oestrogen-only patches, but ensure that the woman still uses the oestrogen-only patches for 2 weeks of the cycle followed by the combined patches for a further 2 weeks, to ensure endometrial protection.
  - **Continuous combined HRT tablets or patches:** reduce the dose gradually every 1–2 months to the lowest strength tablet or patch. Then, take half a tablet or patch daily for a further 1–2 months.
- If symptoms are severe after HRT is stopped or persist for several months after stopping, the woman may wish to restart HRT after reassessment and counselling. Often a lower dose of HRT can be used (e.g. estradiol 1 mg) if HRT is restarted.

Basis for recommendation

- This recommendation is based on published expert opinion [NZGG, 2004; ICSI, 2006].
- In older women, sleep disorders rather than hot flushes may be the major manifestation of renewed menopausal symptoms [ICSI, 2006].

Antidepressants

Which antidepressant should I use?

- Offer a selective serotonin reuptake inhibitor, such as paroxetine, fluoxetine, or citalopram, or a serotonin–norepinephrine reuptake inhibitor, such as venlafaxine:

- There is evidence that paroxetine, fluoxetine, citalopram, and venlafaxine are effective for treating hot flushes, but no evidence that one is more effective than the other.

- All are unlicensed for treating hot flushes.

[Rees and Purdie, 2006a]

What dose should I use?

- Antidepressants are unlicensed for treating menopausal symptoms. However, the following dosages have been assessed and found to be effective for hot flushes in short-term studies:
  - Citalopram 20 mg daily.
  - Paroxetine 20 mg daily.
  - Fluoxetine 20 mg daily.
  - Venlafaxine 37.5 mg twice daily.

What issues do I need to consider before prescribing a selective serotonin reuptake inhibitor?

- The most common adverse effects associated with selective serotonin reuptake inhibitors (SSRIs) are gastrointestinal effects (nausea and diarrhoea), central nervous system effects (dizziness, agitation, insomnia, and tremor), and sexual dysfunction [Taylor et al, 2005].

- Observational studies have shown that SSRIs increase the risk of upper gastrointestinal bleeding, probably by altering platelet function [de Abajo et al, 1999; van Walraven et al, 2001; Dalton et al, 2003; Meijer et al, 2004]. This observed increase in risk may also apply to other types of bleeding:
  - This risk is increased in people who are also taking low-dose aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) [Dalton et al, 2003]. Consider gastroprotection for all people who are prescribed both an SSRI and an NSAID or aspirin [Paton and Ferrier, 2005].
  - This increased risk may also apply to very old people or those with a history of gastrointestinal bleeding. Consider using an antidepressant with a low affinity for the serotonin transporter [Paton and Ferrier, 2005].
  - People receiving warfarin should receive careful coagulation monitoring when treatment with an SSRI is initiated or stopped.

- Extrapyramidal symptoms are relatively rare and seem to be most common with paroxetine [CSM, 2000].

- Co-administration of SSRIs with other serotonergic drugs (e.g. tramadol, triptans) or with dopaminergic drugs (e.g. selegiline) may also increase the risk of serotonin syndrome, and close monitoring is advised [Stockley, 2002].

- SSRIs have a low proconvulsant effect, the seizure risk being dose-related, and are a good choice of antidepressant for people with epilepsy. However, fluoxetine and paroxetine (and to a lesser extent sertraline) can increase serum levels of phenytoin and carbamazepine through inhibition of hepatic enzymes. Serum phenytoin levels should be monitored and the dosage adjusted accordingly when starting, stopping, or changing the dose of these SSRIs. Citalopram is a weak enzyme inhibitor and has a low potential for clinically significant interactions [Taylor et al, 2005].

What issues do I need to consider before prescribing venlafaxine?

- Nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, and asthenia are the most common adverse effects. They are thought to be dose related and transient.

- Do not prescribe venlafaxine for people with:
  - Uncontrolled hypertension.
  - A high risk of serious cardiac arrhythmias.
  - A recent myocardial infarction.
- Prescribe venlafaxine in people with pre-existing hypertension only if their blood pressure is controlled in line with the current National Institute for Health and Clinical Excellence (NICE) guidelines for hypertension. For more information, see the CKS topic on Hypertension - not diabetic.
- Monitor people taking venlafaxine (including those with pre-existing hypertension) for signs and symptoms of cardiac dysfunction and any increase in blood pressure:
  - Check blood pressure on initiation of therapy and regularly during treatment (especially during dose titration). If there is a sustained increase in blood pressure:
  - Reduce the dose *or*
  - Discontinue treatment.

[ABPI Medicines Compendium, 2006; NICE, 2007]

How should I stop an antidepressant?

- **When stopping or reducing the dose of an antidepressant, some people experience such symptoms as dizziness, nausea, paraesthesiae, anxiety, diarrhoea, flu-like symptoms, and headaches.** These symptoms occur with all classes of antidepressants, and are often referred to as discontinuation (or withdrawal) symptoms:
  - Discontinuation symptoms are more common with longer treatment courses and rarely occur with treatments lasting less than 6 weeks.
  - Onset is usually within 5 days of stopping treatment. Occasionally, symptoms occur during tapering or after missed doses.
  - Symptoms are usually mild and self limiting, rarely lasting for more than 1–2 weeks. However, they can be severe, particularly if the drug is stopped abruptly.
  - Discontinuation symptoms are more likely with: antidepressants with a short half-life, such as paroxetine; in people who developed anxiety symptoms at the start of treatment; and in people taking other centrally-acting drugs.
- **Reduce the dose or frequency of antidepressant gradually over 4 weeks:**
  - More rapid discontinuation may be necessary in people with severe adverse reactions to treatment.
  - In people who have been receiving longer-term treatment, taper the dose over 6 months.
- **Fluoxetine can be stopped abruptly if the dose is 20 mg daily,** as it has a long half-life and active metabolites.
- When stopping an antidepressant, ask the person to seek advice if they experience significant discontinuation symptoms.
- **If discontinuation symptoms are mild,** reassure the person that the symptoms usually pass in a few days.
- **If discontinuation symptoms are severe,** consider reintroducing the original antidepressant and then tapering more slowly while monitoring symptoms.

[Anderson et al, 2000; Haddad, 2001; Taylor et al, 2003; NICE, 2004]

Clonidine

What dose of clonidine should I use?

- Use 50 micrograms twice daily and increase to 75 micrograms twice daily after 2 weeks if necessary for vasomotor symptoms (licensed use).

[BNF 54, 2007]

What issues should I consider before prescribing clonidine?

- Hypotension, dizziness, sedation, dry mouth, fluid retention, and nausea are the most common adverse effects.
- Clonidine may also aggravate depression or produce insomnia:
    - Tricyclic antidepressants (TCAs) can antagonize the effects of clonidine, and a higher dose of clonidine (75 micrograms twice daily) may be required.
- Clonidine may potentiate bradyarrhythmic conditions:
    - Avoid in women with sinus bradycardia or atrioventricular block.
    - Avoid concomitant use of beta-blockers or cardiac glycosides if possible.
- There is a risk of rebound hypertension when a beta-blocker or a TCA is stopped in someone taking clonidine. Withdraw the beta-blocker or TCA slowly over a few days to avoid this. Clonidine should also be reduced gradually over a few days if used at high dose.

[ABPI Medicines Compendium, 2002]