27 February 2004

Final Revision 2 of core SPC for HRT products
Conventions:

CORE SPC FOR HORMONE REPLACEMENT THERAPY

Revision 2: adopted revisions of the MRFG for the core SPC for HRT following the restriction of osteoporosis indication to second-line therapy, dated February 2004

Explanatory Notes:

This core SPC for Hormone Replacement Therapy products is intended for treatment of post-menopausal women.

1. When the CPMP Points to Consider on HRT is due for revision, the following recommendation is proposed for inclusion in order to emphasise the current statement included on this point:
   When the indication for a HRT product is extended to include perimenopausal women, the studies must include symptomatic women who have not yet reached menopause but are in the perimenopausal transitional years, marked by irregularity of menstrual cycles and symptoms of oestrogen deficiency. Separate analysis of the benefit/risk is recommended, as in perimenopausal women endogenous oestrogen production has not yet ceased.1 2

2. The following sources were used to accomplish this core SPC for HRT products:
   • SPCs of some mutually agreed HRT products (recent applications);
   • Published literature;
   • Notice to applicants, A guideline on the SPC (included in The Rules governing Medicinal Products in the European Community Volume 2A and 2B The Notice to Applicants)
   • CPMP Note for Guidance on postmenopausal osteoporosis in women (CPMP/EWP/552/95, revision 1 adopted January 2001);
   • CPMP Points to Consider on Hormone Replacement Therapy (CPMP/EWP/021/97).
   • SPC wording for medicinal products used in hormone replacement therapy with regard to venous thrombo-embolism as agreed by the PhVWP in September 2001;
   • SPC wording for medicinal products used in hormone replacement therapy with regard to breast cancer as agreed by the PhVWP in July 2001

4.1 Therapeutic Indications

2 CPMP Points to Consider on HRT

Core SPC HRT revision 2
Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women. For continuous combined oestrogen + progestagen HRT, the trial population should be qualified as 'more than x years post menopause' (depending on the inclusion criteria of the studies submitted in support of this indication).

(When the indication for a HRT product is extended to include perimenopausal women, the studies must include symptomatic women who have not yet reached menopause but are in the perimenopausal transitional years, marked by irregularity of menstrual cycles and symptoms of oestrogen deficiency. Separate analysis of the benefit/risk is recommended, as in perimenopausal women endogenous oestrogen production has not yet ceased. 1, 2)

Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. 3

(See also Section 4.4)

When the target population is wider than the clinical trial population included in the main efficacy studies, this should be mentioned here. For instance: “The experience treating women older than 65 years is limited.” 3 Additional indications could be acceptable if they are based on sufficient clinical data.

4.2 Posology and method of administration

The method of administration should be described as briefly as possible.

Oestrogens + progestagens:

- The terminology for dosing of HRT products should be the following: “Cyclic”: When the oestrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. The progestagen is usually added for 12-14 days of the cycle. “Continuous sequential”: The oestrogen is dosed continuously. The progestagen is usually added for 12-14 days (or more) of every 28 day cycle, in a sequential manner. “Continuous combined”: The oestrogen and the progestagen are given every day without interruption.

- Advice on how to initiate treatment should be given for treatment naive patients and for patients changing from other HRTs (cyclic, sequential or continuous combined).

- When more than one combination of progestagen and oestrogen is available for the same product, advice should be given on a suitable starting dose combination and criteria given

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3 Revised Note for Guidance on the summary of product characteristics, adopted by the CPMP in December 1999
for selecting another dose combination. Such advice should preferably be based on results of clinical studies.

- The section should include the statement:
  “For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used”.

Oestrogen only:

- For oestrogen-only products the indication section should make clear whether the product is indicated only for women without a uterus. For oestrogen-only products licensed for women with a uterus, advice on the addition of a progestagen should be given in section 4.2. Only progestagens approved for addition to oestrogen treatment should be recommended. Generally a progestagen should be added for at least 12-14 days every month/28 day cycle. Depending on the range of progestagen doses licensed for addition in the CMS, the advice could give examples of suitable products and doses.

- Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestagen in hysterectomised women.

- Advice on how to act if a dose is forgotten should be given, including a statement that forgetting a dose may increase the likelihood of break-through bleeding and spotting.

4.3. Contra-indications

- Known, past or suspected breast cancer;
- Known or suspected oestrogen-dependent malignant tumours (e.g endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;
- Known hypersensitivity to the active substances or to any of the excipients;
- Porphyria.

4 SPC wording for medicinal products used in hormone replacement therapy with regard to venous thromboembolism as agreed by the PhVWP in September 2001/September 2002 based on data from the WHI-trial JAMA 2002;288:321-333


4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.\textsuperscript{4,5,7,8,9}

Medical examination/follow-up

- Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see ‘Breast cancer’ below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

- If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with X, in particular:
  - Leiomyoma (uterine fibroids) or endometriosis
  - A history of, or risk factors for, thromboembolic disorders (see below)
  - Risk factors for oestrogen dependent tumours, e.g. 1\textsuperscript{st} degree heredity for breast cancer
  - Hypertension
  - Liver disorders (e.g. liver adenoma)
  - Diabetes mellitus with or without vascular involvement
  - Cholelithiasis
  - Migraine or (severe) headache
  - Systemic lupus erythematosus.
  - A history of endometrial hyperplasia (see below)
  - Epilepsy
  - Asthma
  - Otosclerosis

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy
Endometrial hyperplasia

- The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestagen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.

- **Additional 2nd paragraph for tibolone:**
  The endometrial safety of tibolone is currently uncertain.

- **For oestrogen-only products:**
  For oral doses of estradiol >2mg, conjugated equine oestrogens >1.25 mg and patches >50 ug/day the endometrial safety of added progestagens have not been studied. (This should be explicitly stated for such products.)

- Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

- **Additional warning to be included only in the SPC of oestrogen-only products:**
  “Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestagens to oestrogen replacement therapy is should be considered in women who have undergone hysterectomy because of endometriosis if they are known to have residual endometriosis.”

Breast cancer

A randomised placebo-controlled trial, the Women’s Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestagen combinations or tibolone for HRT for several years (see Section 4.8). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestagen was added, either sequentially or continuously, and regardless of type of progestagen. There was no evidence of a difference in risk between the different routes of administration.

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In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

- HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate =4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.
- Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m\(^2\)) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (eg, painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

- There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement
Study) showed a possible increased risk of cardiovascular morbidity in the first year of 
use and no overall benefit. For other HRT products there are only limited data from 
randomised controlled trials examining effects in cardiovascular morbidity or mortality. 
Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke\(^5\)

- One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an 
  increased risk of ischaemic stroke in healthy women during treatment with continuous 
  combined conjugated oestrogens and MPA. For women who do not use HRT, it is 
  estimated that the number of cases of stroke that will occur over a 5 year period is about 3 
  per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is 
  estimated that for women who use conjugated estrogens and MPA for 5 years, the number 
  of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 
  years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is 
  unknown whether the increased risk also extends to other HRT products.

Ovarian cancer\(^8\)

- Long-term (at least 5-10 years) use of oestrogen-only HRT products in hysterectomised 
  women has been associated with an increased risk of ovarian cancer in some 
  epidemiological studies. It is uncertain whether long-term use of combined HRTs confers 
  to a different risk than oestrogen-only products.

Other conditions

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal 
  dysfunction should be carefully observed. Patients with terminal renal insufficiency 
  should be closely observed, since it is expected that the level of circulating active 
  ingredients in X is increased.

- “Women with pre-existing hypertriglyceridemia should be followed closely during 
  oestrogen replacement or hormone replacement therapy, since rare cases of large increases 
  of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy 
  in this condition.”

- “Estrogens increase thyroid binding globulin (TBG), leading to increased circulating total 
  thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by 
  radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, 
  reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other 
  binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-
  hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and 
  sex steroids, respectively. Free or biological active hormone concentrations are 
  unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, 
  alpha-I-antitrypsin, ceruloplasmin).”

- There is no conclusive evidence for improvement of cognitive function. There is some 
  evidence from the WHII trial of increased risk of probable dementia in women who start 

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\(^8\) Lacey et al JAMA 2002;288:334-341; Riman et al LNCI 2002;94:497-504
using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.9

4.5 Interactions

See the SPC guideline. The following is a model paragraph, which may be modified if interaction studies of the steroids included in the product indicate differences. The magnitude of effect observed for a specific product/type of product could be included. For combination products, specific information for the progestagen should be added.

“The metabolism of oestrogens [and progestagens] may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamezapin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John’s wort (Hypericum Perforatum) may induce the metabolism of oestrogens [and progestagens]. [For transdermal products the following can be added: At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens [and progestagens] might be less affected than oral hormones by enzyme inducers.]

Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.“

4.6 Pregnancy and lactation

1. Products with oestrogens only (2 options)

1.1 Indicated for women without uterus

Not applicable, because [Tradename] is only indicated in women without uterus

1.2 Indicated for women with uterus

[Tradename] is not indicated during pregnancy. If pregnancy occurs during medication with [Tradename] treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects

2. Products with oestrogens/progestagens (4 options)

2.1 Known progestagen (i.e. human data on exposed pregnancies), no particular effect

[Tradename] is not indicated during pregnancy. If pregnancy occurs during medication with [Tradename] treatment should be withdrawn immediately.

Clinically, data on a limited/large number of exposed pregnancies indicate no adverse effects of [progestagen] on the foetus.
The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens + progestagens indicate no teratogenic or foetotoxic effect.

2.2 Known progestagen (i.e. human data on exposed pregnancies), particular effect
[Tradename] is not indicated during pregnancy. If pregnancy occurs during medication with [Tradename] treatment should be withdrawn immediately.
Data on a limited/large number of exposed pregnancies indicate adverse effects of [progestagen] on the foetus [to be specified].
The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of oestrogens + progestagens indicate no teratogenic or foetotoxic effect.

2.3 New progestagen or progestagen without human data; no relevant effects in animal studies
[Tradename] is not indicated during pregnancy. If pregnancy occurs during medication with [Tradename] treatment should be withdrawn immediately.
For [name of the progestagen] no clinical data on exposed pregnancies are available.
Studies in animals have not shown reproductive toxicity.
The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of oestrogens with other progestagens indicate no teratogenic or foetotoxic effect.

2.4 New progestagen or progestagen without human data; potentially relevant effects in animal studies
[Tradename] is not indicated during pregnancy. If pregnancy occurs during medication with [Tradename] treatment should be withdrawn immediately.
For [name of the progestagen] no clinical data on exposed pregnancies are available.
Studies in animals have shown reproductive toxicity (see 5.3). The potential risk for humans is unknown.
The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens with other progestagens indicate no teratogenic or foetotoxic effect.

Lactation:
[Tradename] is not indicated during lactation.

4.8. Undesirable effects
This section should follow the CPMP Note for Guidance on the SPC. Specifically it should contain:
• An introductory paragraph providing an estimate of the overall percentage of treated patients expected to experience adverse reactions and a mention of all adverse reactions appearing in ≥10% of patients in clinical trials.

• Following the introductory paragraph, a table should be included, in which all Adverse Drug Reactions (ADRs) found in clinical trials of the product should be noted. This table should have the following format:
MedDRA High Level Terms and specific Preferred Term ADRs can be used in this table. ADRs to be included under “rare events” are to be found among class-effects of oestrogens.

Breast cancer
According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women’s Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For oestrogen-only HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI 1.21 – 1.49) and 1.30 (95%CI 1.21 – 1.40), respectively.

For oestrogen plus progestagen combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

The MWS reported that, compared to never users, the use of various types of oestrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of oestrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI 1.01 – 1.54) after 5.6 years of use of oestrogen-progestagen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:
- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 current or recent users of HRT, the number of additional cases during the corresponding period will be
  - For users of oestrogen-only replacement therapy
    - between 0 and 3 (best estimate = 1.5) for 5 years’ use
    - between 3 and 7 (best estimate = 5) for 10 years’ use.
  - For users of oestrogen plus progestagen combined HRT,
    - between 5 and 7 (best estimate = 6) for 5 years’ use
    - between 18 and 20 (best estimate = 19) for 10 years’ use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an additional 8 cases of invasive breast cancer would be due to oestrogen-progestagen combined HRT (CEE + MPA) per 10,000 women years.

According to calculations from the trial data, it is estimated that:
For 1000 women in the placebo group,
- about 16 cases of invasive breast cancer would be diagnosed in 5 years.

For 1000 women who used oestrogen + progestagen combined HRT (CEE + MPA),
the number of additional cases would be
- between 0 and 9 (best estimate = 4) for 5 years’ use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4).’

Endometrial cancer 10 [additional text for tibolone in brackets]

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestagen to oestrogen-only therapy greatly reduces this increased risk.

[The endometrial safety of tibolone is uncertain]

- The table is to be followed by very rare ADRs, —(usually class-effects), common to all HRT products and specific texts generated by the PhVWP or other relevant groups.

Example of a post-tabular text:
Other adverse reactions have been reported in association with oestrogen/progestagen treatment:
- Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer.
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see section 4.3 Contraindications and 4.4 Special warnings and precautions for use.
- Myocardial infarction and stroke
- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia (see section 4.4)

5.1 Pharmacodynamic properties

• **Estradiol/Estradiol valerate:** The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy. *(Note: only for products with the osteoporosis prevention indication)*

or:

**Conjugated equine oestrogens:** The active ingredients are primarily the sulphate esters of estrone, equilin sulphates and 17α/β- estradiol.¹¹ These substitute for the loss of oestrogen production in menopausal women, and alleviate menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy *(Note: only for products with the osteoporosis prevention indication)*

• **Progestagen:**
  As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

*All other information in this section should be restricted to the indications approved and potential adverse events (see comment below on lipids).*

**Clinical trial information**

• Relief of oestrogen-deficiency symptoms and bleeding patterns
  - Relief of menopausal symptoms was achieved during the first few weeks of treatment.
  - Regular withdrawal bleeding occurred in x% of women with a mean duration of x days. Withdrawal bleeding usually started x days before/after the last pill of the progestagen phase. Break through bleeding and/or spotting appeared in x% of the women during the first three months of therapy and in x% during months 10-12 of treatment. Amenorrhoea (no bleeding or spotting) occurred in x% of the cycles during the first year of treatment (for cyclic or sequential products).
  - or: Amenorrhoea was seen in x% of the women during months 10-12 treatment. Bleeding and/or spotting appeared in x% of the women during the first three months of treatment and in x% during months 10-12 of treatment (for continuous combined products).

• Prevention of osteoporosis
  - Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.
  - Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestagen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also

¹¹ Goodman and Gilman’s The pharmacological basis of Therapeutics, 9th edition
prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.
- After … years of treatment with X, the increase in lumbar spine bone mineral density (BMD) was \( x \pm x \% \) (mean \( \pm SD \)). The percentage of women who maintained or gained BMD in lumbar zone during treatment was \( x\% \).
- X also had an effect on hip BMD. The increase after … years was \( x\% \pm x\% \) (mean \( \pm SD \)) at femoral neck and \( x \pm x\% \) (mean \( \pm SD \)) at total hip. The percentage of women who maintained or gained BMD in hip zone during treatment was \( x\% \).

- Information on biochemical markers of bone resorption and formation should not be included. BMD is considered a better surrogate endpoint for fracture than biochemical markers.
- Information on serum lipids (all products)
  Changes in lipids should not be included, as this information is not related to any of the present indications for HRT. Considering that no benefit has been demonstrated in primary and secondary prevention of coronary artery disease, the clinical relevance of lipid changes is unknown and the relevance for the safety of the product therefore highly questionable.

5.2 Pharmacokinetic properties
See the Note for Guidance on the SPC.
- For all HRT products, this section should include figures on \( C_{\text{max}} \), \( C_{\text{average}} \), \( C_{\text{min}} \) (trough) plasma levels on the oestrogen and progestagen.

5.3 Preclinical safety data
No specific recommendations. This section should conform with the CPMP Guideline on the Summary of Product Characteristics. Only results relevant to the prescriber should be mentioned.
When animal studies have indicated embryotoxic or other effects, this observation should be discussed here, with cross-reference to section 4.6.