CORE SPC FOR HORMONE REPLACEMENT THERAPY PRODUCTS

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4.1 Therapeutic Indications

- Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women.

  – Sequential HRT regimen: HRT for oestrogen deficiency symptoms [in women at least 6 months since last menses*1];

  – Continuous combined HRT regimen: HRT for oestrogen deficiency in women x months (years) since last menses (depending on the inclusion criteria of the studies submitted in support of this indication).

- 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. (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.

- 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.

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.

1 **required for all sequential HRT products other than those with sufficient data to demonstrate efficacy and safety in peri-menopausal women*

"**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 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 or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- 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.

4.4 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.

- Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

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 appropriate imaging tools, e.g. 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
  - Risk factors for thromboembolic disorders (see below)
  - Risk factors for oestrogen dependent tumours, e.g. 1st 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 and carcinoma

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2-to 12-fold greater compared

with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

- The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

- ***Additional warning for oestrogen-only products****:*
  For oral doses of estradiol >2mg, conjugated equine oestrogens >0.625 mg and patches >50 ug/day the endometrial safety of added progestagens has not been demonstrated. ***(****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 should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis***."**

Breast cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestagen therapy

- The randomised placebo-controlled trial the (Women's Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years (see Section 4.8).

Oestrogen-only therapy

- The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

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

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller, risk (see Section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).

- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

- Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.
  As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).
  If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g, antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

- 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 (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

- There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT.

  Combined oestrogen-progestagen therapy
  The relative risk of CAD during use of combined oestrogen+progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

  Oestrogen-only
  Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic stroke

- Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Other conditions

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridaemia 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.
- Oestrogens 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).
- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

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] HRT 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 foetal 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 foetal 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:

Organ system class (e.g. MedDRA SOC level)	Common ADRs, >1/100, < 1/10	Uncommon ADRs, >1/1,000, <1/100	Rare ADRs >1/10,000, <1/1000

- MedDRA High Level Terms and specific Preferred Term ADRs can be used in this table.

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period*2	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
		Oestrogen only HRT	
50-65	9-12	1.2	1-2 (0-3)
		Combined oestrogen-progestagen	
50-65	9-12	1.7	6 (5-7)

#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.
the TC we finally decided to re-include the figures of table 2 of the Million Women study.

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
		CEE oestrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*3
		CEE+MPA oestrogen & progestagen‡	
50-79	~~14~~ 17	1.2 (1.0 – 1.5)	+4 (0 – 9)

‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Endometrial cancer risk

Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1000 women with an uterus not using HRT.

*2 *Taken from baseline incidence rates in developed countries*
*3 *WHI study in women with no uterus, which did not show an increase in risk of breast cancer*

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).
Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral oestrogen-only*4			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined oestrogen-progestagen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 - 13)

Risk of coronary artery disease

- The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen + progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

- This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke*5 over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1-1.6)	3 (1-5)

*4 *Study in women with no uterus*

5**no differentiation was made between ischaemic and haemorrhagic stroke.*

- The adverse event table is to be followed by ADRs, (usually class-effects), common to all HRT products.

  Example of a post-tabular text:

  Other adverse reactions have been reported in association with oestrogen/progestagen treatment:

  – Gall bladder disease.
  – Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
  – Probable dementia over the age of 65 (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. 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**.** Irregular 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 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 ± x % (mean ± 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% ± x% (mean ± SD) at femoral neck and x ± x% (mean ± 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_{max}, $C_{average}$, C_{min} (trough) plasma levels on the oestrogen and progestagen.

5.3 Preclinical safety data

No specific recommendations. This section should conform to 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.