Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the Summary of Product Characteristics and package leaflet are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

A. Summary of product characteristics

- **Section 1 Name of the medicinal product**

[The strength should be expressed as micrograms/g in this section]

{(Invented) name strength (in micrograms/g)[1] pharmaceutical form}

[…]

- **Section 4.1 Therapeutic indications**

[Any sentences should be removed from this section and the following should be added]

Treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women.

The experience treating women older than 65 years is limited.

- **Section 4.2 Posology and method of administration**

[The text below should be inserted by replacing the existing text of this section]

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.

Route of administration:

cream for vaginal use

[invented name] should be applied with an applicator.

The applicator should be cleaned with warm water each time after use.

Treatment may be started on any convenient day.

[Invented name] should not be used immediately prior to sexual intercourse or as a lubricant, in order to avoid possible undesirable effects in the partner.

Using [invented name] together with latex products (e.g. condoms, diaphragms) can reduce the functionality of such products thereby making them less reliable as [invented name] contains excipients (other ingredients, particularly stearates).

Initial dose: One filled applicator dose (= 2 g cream) is inserted before retiring to bed. The cream should be applied on every other day, i.e. at 48-hourly intervals for one week.

Maintenance dose for up to 2-4 weeks: One filled applicator dose (= 2 g cream) is inserted before retiring to bed twice weekly.

[invented name] should be used for a single treatment period up to 4 weeks.

The endometrial safety of prolonged treatment and repeated treatment courses is unknown. Given that systemic exposure occurs during treatment with [Invented name], prolonged treatment beyond 4 weeks is not recommended. No addition of a progestogen is needed when using [invented name] for 4 weeks or less. If symptoms persist beyond 4 weeks, alternative therapies should be considered.

[1] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/compilation-quality-review-documents-decisions-stylistic-matters-product-information_en.pdf

If unexpected bleeding should occur, treatment with [invented name] must be suspended until the cause of bleeding has been clarified (see section 4.4 on endometrial safety).

If a dose is forgotten, it should be taken as soon as the patient remembers. A double dose should be avoided.

The experience treating women older than 65 years is limited.

Paediatric population

[invented name] should not be used in children and adolescents.

- **Section 4.3 Contraindications**

[The text below should be inserted by replacing the existing text of this section]

[invented name] should not be used in the following cases:

- 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
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Porphyria.

- **Section 4.4 Special warnings and precautions for use**

[The text below should be inserted by replacing the existing text of this section]

For the treatment of postmenopausal symptoms, Hormone Replacement Therapy (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.

[Invented name] should not be used in patients who are treated with systemic HRT.

During treatment with [invented name], an increase in plasma oestradiol levels above the physiological range of postmenopausal women is observed.

Therefore, for safety reasons, the maximum duration of treatment is limited to 4 weeks. Vigilance is required for possible systemic effects.

Medical examination/follow-up

Before initiating or reinstituting hormone therapy, a complete personal and family medical history should be obtained. 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. 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 oestrogen treatment, 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 systemic oestrogen-only users varies from 2- to 12-fold compared with non-users,

depending on both duration of treatment and on oestrogen dose. After stopping treatment risk remain elevated for at least 10 years.

Risk estimates have been drawn from systemic exposure (HRT). The endometrial safety of [invented name] during prolonged treatment and repeated treatment courses has not been investigated in clinical studies and is therefore unknown. Given that systemic exposure occurs during treatment with [invented name], prolonged treatment beyond the maximum of a single treatment duration of 4 weeks is not recommended (see section 4.2).

If bleeding or spotting appears at any time on therapy, or continues after treatment, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

The woman should be advised to contact her doctor in case bleeding or spotting occurs during treatment with [invented name].

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially 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.

The WHI trial found no increase in 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 found in users of oestrogen-progestagen combinations.

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.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with 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.

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 to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery stopping [invented name] is recommended. In women with no personal history of VTE but with 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.

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 increase with age.

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 biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

HRT does not improve cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

Local adverse events

The intravaginally applied applicator may cause minor local trauma, especially in women with serious vaginal atrophy.

Excipients benzyl alcohol and cetyl stearyl alcohol

[For Montavit products only the following sentence should be used instead the above sentence]

Excipients benzyl alcohol, cetyl stearyl alcohol and propylene glycol

This medicine contains [amount in mg] benzyl alcohol per application dose. Benzyl alcohol may cause mild local irritation.
This medicine contains cetyl stearyl alcohol which can cause local skin irritation (e.g. contact dermatitis).

[For Montavit products should additionally state here]

This medicine contains [amount in mg] propylene glycol per application dose

- **Section 4.5 Interaction with other medicinal products and other forms of interaction**

[The text below should be inserted by replacing the existing text of this section]

Interactions of [invented name] with other medicinal products were not investigated.

However, the metabolism of oestrogens 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, carbamazepine) 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.

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

At vaginal administration, the first-pass effect in the liver is avoided and, thus, vaginally applied oestrogens might be less affected than oral hormones by enzyme inducers.

- **Section 4.6 Fertility, pregnancy and lactation**

[The text below should be inserted in this section and the existing text should be deleted]

Pregnancy

[invented name] is not indicated during pregnancy. If pregnancy occurs during medication with [invented name], 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 effect.

Lactation

[invented name] should not be used during breast feeding.

- **Section 4.7 Effects on ability to drive and use machines**

[The text below should be inserted in this section and the existing text should be deleted]

[invented name] is unlikely to have any effect on alertness or coordination.

- **Section 4.8 Undesirable effects**

[The text below should be inserted in this section and the existing text should be deleted]

Post-marketing experience

The following undesirable effects related to [invented name] have been reported:

System organ class (MedDRA)	Uncommon (≥ 1/1,000 to < 1/100)	Very rare (< 1/10,000),
General disorders and administration site conditions	Transient, mild local irritation (e.g. pruritus, burning). Slight discharge	Hypersensitivity skin reaction (allergic contact eczema)

The following adverse reactions have been associated with oral and/or transdermal oestrogen therapy (class effects):

System Organ Class	Common ≥ 1/100 to < 1/10 (≥ 1% and <10%	Uncommon > 1/1000 to <1/100 (> 0.1% and <1%)
Infections and infestations		Vaginitis, including vaginal candidiasis
Immune system disorders		Hypersensitivity
Psychiatric disorders	Depression	Changes in libido, mood disturbances
Nervous system disorders		Dizziness, headache, migraine, anxiety
Eye disorders		Intolerance to contact lenses
Vascular disorders		Venous thrombosis, pulmonary embolism
Gastrointestinal disorders		Nausea, bloating, abdominal pain
Hepatobiliary disorders		Gallbladder disease

Skin and subcutaneous tissue disorders	Alopecia	Chloasma/melasma, hirsutism, pruritus, rash
Musculoskeletal, connective tissue and bone disorders	Arthralgias, leg cramps	
Reproductive system and breast disorders	Abnormal uterine bleeding (breakthrough bleeding/spotting), breast pain, breast tenderness, breast enlargement, breast discharge, leukorrhoea	
General disorders and administration site conditions		Oedema
Investigations	Changes in weight (increase or decrease), increased triglycerides	

Other risks

Other adverse reactions have been reported in association with oestrogen/progestogen treatment.

- Skin and subcutaneous disorders: erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (see section 4.4)
- Gallbladder disease

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen 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-progestogen 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 users of HRT over 5 year period***	**Risk ratio#**	**Additional cases per 1000 HRT user 5 years (95% CI)**
		Oestrogen-only HRT	
50 – 65	9 – 12	1.2	1 – 2 (0 – 3)
		Combined oestrogen-progestogen	
50 – 65	9 – 12	1.7	6 (5 – 7)
* Taken from baseline incidence rates in developed countries. # Overall risk ratio. The risk ratio is not constant but will increase with increasing duration of use			

Age range (years)	Additional cases per 1000 users of HRT over 5 year period*	Risk ratio#	Additional cases per 1000 HRT user 5 years (95% CI)
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

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

Age range (years)	Incidence per 1000 women placebo arm over 5 year period	Risk ratio and 95% CI	Additional cases per 1000 HRT user 5 years (95% CI)
		CEE oestrogen-only	
50 – 79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA oestrogen & progestogen #	
50 – 79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)
* WHI study in women with no uterus, which did not show an increase in risk of breast cancer. # 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 non-users.			

Endometrial hyperplasia and carcinoma

Postmenopausal women with a uterus

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

Ovarian cancer

Use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

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 placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 users
Oral oestrogen only*			
50 – 79	7	1.2 (0.6 – 2.4)	1 (-3 – 10)
Oral combined oestrogen-progestogen			
50 – 79	4	2.3 (1.2 – 4.3)	5 (1 –13)
**Study in women with no uterus*			

Risk of coronary artery disease

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

Risk of ischaemic stroke

The use of oestrogen-only and combined oestrogen-progestogen 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* over 5 years' use

Age range (years)	**Incidence per 1000 women placebo arm over 5 years**	**Risk ratio and 95% CI**	**Additional cases per 1000 users over 5 years**
50 – 59	8	1.3 (1.1 – 1.6)	3 (1 –5)
**No differentiation was made between ischaemic and haemorrhagic stroke*			

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

*[*For the printed material, please refer to the guidance of the annotated QRD template.]*

- **Section 4.9 Overdose**

[The text below should be inserted in this section. Any existing section should be deleted.]

Undesirable effects - such as gastrointestinal complaints, nausea, etc. - may occur after accidental or intentional administration of large amounts of [invented name]. Treatment is symptomatic.

- **Section 5.1 Pharmacodynamic properties**

[…]

[The text below should be inserted in this section.]

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol.

Vaginally applied oestrogen alleviates the symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women.

Relief of vaginal symptoms was achieved during the first 4 weeks of treatment.

- **Section 5.2 Pharmacokinetic properties**

[The text below should be inserted in this section. Any existing section should be deleted.]

When applied vaginally, estradiol is absorbed from the vaginal epithelium and enters the bloodstream in concentrations which are above the postmenopausal range.

The following values were determined after single-dose administration of 2 g [invented name], equivalent to 200 mcg E2: AUC_{0-36}= 1285.2 pg/ml*h and C_{max} = 103.5 pg/ml. The geometric mean half-life of E2 was 5.05 hours, with high interindividual variability.

In four-week multiple-dose study, mean estradiol serum concentration at baseline and trough concentration, (estimated about 36 hours after the last administration of study medication) were 6.4 pg/ml and 15.1pg/ml, respectively. No C_{max} levels were measured in this study.

Estradiol is rapidly metabolised in the liver and intestinal tract to estrone and subsequently to estriol. Estradiol conversion to estriol is irreversible. Over 95% of estriol is excreted in the urine, mainly in the form of glucuronides.

- **Section 5.3 Preclinical safety data**

[The text below should be inserted in this section. Any existing section should be deleted.]

17β-Estradiol is a well-known substance. Nonclinical studies provided no additional data of relevance to clinical safety beyond those already included in other sections of the SmPC.

B. Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE INNER (IMMEDIATE) PACKAGING

{NATURE/TYPE}

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength (in micrograms/g) pharmaceutical form}

{Active substance(s)}

[…]

Text to appear on the outer packaging

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[The text below should be inserted in a box in this section]

Only use for maximum of 4 weeks

[…]

Text to appear on the inner (immediate) packaging

5. OTHER

[The text below should be inserted in a box in this section]

Only use for maximum of 4 weeks

C. Package leaflet

- **Section 1: What [invented name] is and what it is used for**

[The text below should be inserted in this section]

[invented name] belongs to a group of medicines called vaginal Hormone Replacement Therapy (HRT).

It is used to relieve menopausal symptoms in the vagina such as dryness or irritation. In medical terms this is known as 'vaginal atrophy'. It is caused by a drop in the levels of oestrogen in your body. This happens naturally after the menopause.

[invented name] works by replacing the oestrogen which is normally produced in the ovaries of women. It is inserted into your vagina, so the hormone is released where it is needed. This may relieve discomfort in the vagina.

- **Section 2: What you need to know before you use [invented name]**

[The currently existing text should be deleted from this section and be replaced by the text below]

During treatment with [invented name], there is an increase in plasma estradiol levels above the physiological range of postmenopausal women. Therefore, for safety reasons, you should use [invented name] no longer than 4 weeks.

Do not use [invented name] when you use other HRT products such as estrogen tablets, patches or gel for treatment of hot flushes or prevention of osteoporosis.

Medical history and regular check-ups

The use of HRT carries risks which need to be considered when deciding whether to start taking [invented name], or whether to carry on taking it.

Before you start HRT, your doctor will ask about your own and your family's medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or internal examination, if necessary.

Go for regular breast screening as recommended by your doctor.

- **Do not use [invented name] if**

any of the following applies to you. If you are not sure about any of the points below, talk to your doctor before using [invented name].

Do not use [invented name] if

- You are allergic (hypersensitive) to estradiol or any of the other ingredients of [invented name] (listed in Section 6 Further information)
- You have or have ever had breast cancer, or you are suspected of having it
- You have or have ever had cancer which is sensitive to oestrogens, such as cancer of the womb lining (endometrium), or you are suspected of having it
- You have any unexplained vaginal bleeding
- You have excessive thickening of the womb lining (endometrial hyperplasia) that is not being treated

- You have or have ever had a blood clot in a vein (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism)
- You have a blood clotting disorder (such as protein C, protein S, or antithrombin deficiency)
- You have or have recently had a disease caused by blood clots in the arteries, such as a heart attack, stroke or angina
- You have or have ever had a liver disease and your liver function tests have not returned to normal
- You have a rare blood problem called "porphyria", which is passed down in families (inherited).

If any of the above conditions appear for the first time while using [invented name], stop using it at once and consult your doctor immediately.

- **When to take special care with [invented name]**

Tell your doctor if you have or have ever had any of the following problems before you start the treatment, as these may return or become worse during treatment with <invented name>. If so, you should see your doctor more often for check-ups:

- fibroids inside your womb;
- growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia);
- increased risk of developing blood clots (see "Blood clots in a vein (thrombosis)");
- increased risk of getting a oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer);
- high blood pressure;
- a liver disorder, such as a benign liver tumour;
- diabetes;
- gallstones;
- migraine or severe headaches;
- a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE);
- epilepsy;
- asthma;
- a disease affecting the eardrum and hearing (otosclerosis);
- a very high level of fat in your blood (triglycerides);
- fluid retention due to cardiac or kidney problems;

- **Stop using [invented name] and see a doctor immediately**

If you notice any of the following when taking HRT:

- any of the conditions mentioned in the 'DO NOT take [invented name]' section;
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease;
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness);
- migraine-like headaches which happen for the first time;
- if you become pregnant;
- if you notice signs of a blood clot, such as:
    - painful swelling and redness of the legs;
    - sudden chest pain;
    - difficulty in breathing;

For more information, see 'Blood clots in a vein (thrombosis)'

HRT and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

Taking oestrogen-only HRT will increase the risk of developing excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer).

No addition of a progestagen is needed when using [invented name] for 4 weeks or less. However, when taking [invented name] for a longer period than recommended, the risk of excessive lining of the womb is unknown.

If you get bleeding or drops of blood (spotting), or if these bleedings carry on when you have stopped taking [invented name], you should make an appointment to see your doctor. It could be a sign that your endometrium has become thicker.

Breast cancer

Evidence suggests that taking combined oestrogen-progestagen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

For women who have had their womb removed and who are using oestrogen-only HRT for 5 years, little or no increase in breast cancer risk is shown.

Compare

Women aged 50 to 79 who are not taking HRT, on average, 9 to 17 in 1000 will be diagnosed with breast cancer over a 5-year period. For women aged 50 to 79 who are taking oestrogen-progestagen HRT over 5 years, there will be 13 to 23 cases in 1000 users (i.e. an extra 4 to 6 cases).

Regularly check your breasts. See your doctor if you notice any changes such as:

- dimpling of the skin

- changes in the nipple

- any lumps you can see or feel

Additionally, you are advised to join mammography screening programs when offered to you. For mammogram screening, it is important that you inform the nurse/healthcare professional who is actually taking the x-ray that you use HRT, as this medication may increase the density of your breasts which may affect the outcome of the mammogram. Where the density of the breast is increased, mammography may not detect all lumps.

Ovarian cancer

Ovarian cancer is rare - much rarer than breast cancer. The use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer.

The risk of ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2000 users (i.e. about 1 extra case).

Effect of HRT on heart and circulation

Blood clots in a vein (thrombosis)

The risk of blood clots in the veins is about 1.3 to 3- times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

You are more likely to get a blood clot in your veins as you get older and if any of the following applies to you. Inform your doctor if any of these situations applies to you:

- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, If you need to have surgery);
- you are seriously overweight (BMI >30 kg/m^2);
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots;
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ;
- you have systemic lupus erythematosus (SLE);
- you have cancer;

For signs of a blood clot, see "Stop taking [invented name]" and see a doctor immediately".

Compare

Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1000 would be expected to get a blood clot in a vein.

For women in their 50s who have been taking oestrogen-progestogen HRT for over 5 years, there will be 9 to 12 cases in 1000 users (i.e.an extra 5 cases).

For women in their 50s who have had their womb removed and have been taking oestrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1000 users (i.e. 1 extra case).

Heart disease (heart attack)

There is no evidence that HRT will prevent a heart attack.

Women over the age of 60 years who use oestrogen-progestagen HRT are slightly more likely to develop heart disease than those not taking any HRT.

For women who have had their womb removed and are taking oestrogen-only therapy there is no increased risk of developing a heart disease.

Stroke

The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Compare

Looking at women in their 50s who are not taking HRT, on average, 8 in 1000 would be expected to have a stroke over a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1000 users, over 5 years (i.e. 3 extra cases).

Other conditions

HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Local adverse events

The intravaginally applied applicator may cause minor local injury.

Children and adolescents

[invented name] should not be used in children and adolescents.

- **Other medicines and [invented name]**

Interactions of [invented name] with other medicinal products were not investigated.

Please tell your doctor or pharmacist if you are taking or have recently taken or might take / use any other medicines, including medicines obtained without a prescription, herbal medicines or other natural products.

Some medicines may interfere with the effect of [invented name]. This might lead to irregular bleeding. This applies to the following medicines:

- medicines for epilepsy (e.g. barbiturates, phenytoin and carbamazepine)
- medicines for tuberculosis (e.g. rifampicin and rifabutin)
- medicines to treat HIV infection (e.g. nevirapine, efavirenz, nelfinavir and ritonavir)
- herbal medicines containing St. John's wort (*Hypericum perforatum*)

Laboratory tests

If you need a blood test, please tell your doctor or the laboratory staff that you are taking [invented name], as this medicine may affect the results of some laboratory tests.

- **Pregnancy and breast-feeding**

[Invented name] is for use in postmenopausal women only. If you become pregnant, stop using [invented name] and contact your doctor. [Invented name] should not be used during breastfeeding.

- **Driving and using machines**

No known effect.

[invented name] contains benzyl alcohol and cetostearyl alcohol

[for Montavit products the following sentence should be used instead]

[invented name] contains benzyl alcohol, cetyl alcohol and propylene glycol

This medicine contains [amount in mg] mg benzyl alcohol per application dose. Benzyl alcohol may cause mild local irritation.

Cetostearyl alcohol may cause local skin irritation (e.g. contact dermatitis).

[for Montavit products the following sentence should be added]

This medicine contains [amount in mg] propylene glycol per application dose. Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects. Propylene glycol may cause skin irritation.

- **Section 3: How to use [invented name]**

[The text below should be inserted in this section and any existed text should be deleted]

Always use [invented name] exactly according to the instructions given in this leaflet. You should check with your doctor or pharmacist if you are not sure.

Your doctor will aim to prescribe the lowest dose to treat your symptom for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

- You can start using [invented name] on any day which is best for you.
- [invented name] is a cream for vaginal use.
- [invented name] should be applied in the vagina with an applicator.
- The applicator should be cleaned with warm water each time after use.
- In case the applicator is damaged you should not use it and inform the manufacturer.
- Do not use [invented name] immediately before sexual intercourse or as a lubricant, to prevent possible side effects in your partner.

- Take special care when using [invented name] together with latex products (e.g. condoms, diaphragms), as it contains excipients (other ingredients, particularly stearates) which can reduce the functionality of such products, thereby making them less reliable.
- If your vaginal skin is very vulnerable, be careful when inserting the applicator into the vagina.

How much to use

- First week of treatment:

  Insert the contents of 1 filled applicator (= 2 g cream) before bedtime every other day (leave two days between each dose),

- Second to fourth week of treatment:

  Insert the contents of 1 filled applicator (= 2 g cream) before bedtime twice a week (leave 3 or 4 days between each dose),

Do not use [invented name] for more than 4 weeks. Do not use up any remaining content after completing treatment course.

[In this section the use of the cream with the applicator is inserted. This part of section 3 has not been modified during this procedure]

[…]

[The following text should be inserted after the section "Clean the applicator after use"]

How long should you go on using [invented name]?

[Invented name] should not be used for more than 4 weeks.

It is unknown whether prolonged treatment or repeated treatment courses will cause thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb (endometrial cancer). Therefore, prolonged treatment beyond 4 weeks is not recommended. If symptoms of vaginal atrophy persist beyond 4 weeks, alternative therapies should be considered. Please talk to your doctor.

If you get bleeding or drops of blood (spotting), or if these bleedings carry on when you have stopped taking [invented name], you should make an appointment to see your doctor. It could be a sign that your endometrium has become thicker.

- **If you use more [invented name] than you should**

If you use too much [invented name] on one occasion, side effects such as nausea may occur. Talk to a doctor or pharmacist.

- **If you forget to use [invented name]**

Do not use a double dose of [invented name] to make up for a forgotten single dose. Continue with your treatment as normal.

- **If you stop using [invented name]**

Your doctor will explain the effects of stopping treatment and when to stop it. He or she will also discuss other possibilities for treatment with you.

- **If you need to have surgery**

If you are going to have a surgery, tell the surgeon that you are taking [invented name]. You may need to stop taking [invented name] (see section 2, Blood clots in a vein).

- **Section 4: Possible side effects**

[The text below should be inserted in this section and any existed text should be deleted]

The following diseases are reported more often in women using HRT medicines compared to women not using HRT:

- breast cancer

- abnormal growth or cancer of the lining of the womb (endometrial hyperplasia and carcinoma)

- ovarian cancer

- blood clots in the veins of the legs of lungs (venous thromboembolism)

- heart disease

- stroke

- probable memory loss if HRT is started over the age of 65

For more information about these side effects, see Section 2.

Like all medicines, [invented name] can cause side effects, although not everybody gets them.

The following categories are used to express the frequency of side effects:

Very common:	more than 1 in 10 patients treated
Common:	1 to 10 patients treated out of 100
Uncommon:	1 to 10 patients treated out of 1,000
Rare:	1 to 10 patients treated out of 10,000
Very rare:	less than 1 in 10,000 patients treated
Not known:	frequency cannot be estimated from the available data

Uncommon: temporarily mild local irritation (e.g. itching, burning) and slight discharge may occur.

Very rare: allergic reactions.

[This following sentence should be amended]

The following side effects have been reported with other HRTs:

- Gall bladder disease

- Various skin disorders:

- discoloration of the skin especially of the face or neck known as "pregnancy patches (chloasma)

- painful reddish skin nodules (erythema nodosum)

- rash with target-shaped reddening or sores (erythema multiforme)

Common

Depression, hair loss, joint pain, leg cramps, abnormal uterine bleeding, breast pain, breast tenderness, breast enlargement, breast discharge, weight increase or decrease, increased blood fats (triglycerides)

Uncommon

Vaginitis including infection of the genitals caused by a fungus, changes in sexual drive, mood disturbances, dizziness, headache, migraine, anxiety, intolerance to contact lenses, blood clots in a vein (thrombosis), nausea, bloating, abdominal pain, hirsutism, pruritus, rash, oedema

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse> . This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

[*For the printed material, please refer to the guidance of the annotated QRD template.]

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.