4.2 Posology and method of administration

For oral use.

Treatment is a continuous combined regimen. One combined estradiol / trimegestone tablet is taken daily without interruption.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used (see also section 4.4). Patients should be reevaluated periodically to determine if treatment for symptoms is still necessary.

The tablets are to be swallowed whole, with water and can be taken during or between meals.

In women who are not taking hormone replacement therapy or women who switch from another continuous combined hormone replacement therapy product, treatment may be started on any convenient day. In women transferring from a sequential hormone replacement therapy regimen, treatment should begin the day following completion of the prior regimen.

Posology in women with renal insufficiency

There are no special dosage requirements in case of mild to moderate renal insufficiency. Subjects with severe renal insufficiency (creatinine clearance < 30 ml/min/1.73 m2) have not been studied extensively; therefore, dosage recommendations cannot be given for this patient population (see section 4.4).

Posology in women with hepatic insufficiency

Treatment is contraindicated in women with acute or chronic liver disease (see section 4.3).

Forgotten tablet

If one tablet is forgotten, it should be taken within 12 hours of when normally taken; otherwise, the tablet should be discarded, and the usual tablet should be taken the following day. If one or several tablets are forgotten, the risk for break-through bleeding or spotting is increased.

4.3 Contraindications

Known, past or suspected breast cancer
Known, or suspected oestrogen-dependent malignant tumour (e.g., endometrial cancer)
Undiagnosed genital bleeding
Untreated endometrial hyperplasia
Previous idiopathic or current venous thromboembolic disease (deep venous thrombosis, pulmonary embolism)
Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction, stroke)
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
Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4)

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.

HRT has been associated with increased risks of certain cancers and cardiovascular diseases.

HRT should not be initiated or continued to prevent cardiovascular disease or dementia.

The benefit and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Oestrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

There are additional and/or increased risks that may be associated with the use of combination oestrogen-plus-progestin therapy compared to using oestrogen-alone regimens. These include an increased risk of myocardial infarction, pulmonary embolism, invasive breast cancer and ovarian cancer.

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 Totelle 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. first 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 contraindication 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

Cardiovascular risk

Hormone Replacement Therapy (HRT) has been associated with an increased risk of myocardial infarction (MI) as well as stroke, venous thrombosis and pulmonary embolism (PE).

Estrogen Replacement Therapy (ERT) has been reported to increase the risk of stroke and deep venous thrombosis (DVT).

Patients who have risk factors for thrombotic disorders should be kept under careful observation.

Stroke

In the oestrogen-plus-progestin substudy of Women's Health Initiative (WHI), a statistically significant increased risk of stroke was reported in women receiving the oestrogen/progestin combination compared to women receiving placebo (33 vs. 25 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted.

Should a stroke occur or be suspected, oestrogens should be discontinued immediately.

In the WHI oestrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily conjugated estrogens (CE [0.625 mg]) compared to women in the same age group receiving placebo (45 vs. 33 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted.

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with CE and medroxyprogesterone (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 1,000 women aged 50-59 years and 11 per 1,000 women aged 60-69 years. It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1,000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1,000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Coronary heart disease

In the oestrogen-plus-progestin substudy of WHI, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as non-fatal MI, silent MI or death, due to CHD) in women receiving the oestrogen/progestin combination compared to women receiving placebo (41 vs. 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5.

In the oestrogen-alone substudy of WHI no overall effect on CHD events was reported in women receiving oestrogen alone compared to placebo.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE 0.625 mg compared to placebo) in women with less than 10 years since menopause (8 vs. 16 per 10,000 women-years).

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with oral conjugated equine oestrogens plus medroxyprogesterone acetate demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with oral conjugated equine oestrogens plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year one, but not during the subsequent years.

From the original HERS trial, 2,321 women agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the hormone-treated group and the placebo group in the HERS, the HERS II, and overall.

Venous thromboembolism

Epidemiological studies have found an increased risk of venous thromboembolism (VTE) in users of ERT/HRT who did not have predisposing conditions for VTE. These studies found the VTE risk to be about one case per 10,000 women per year among healthy women not using ERT/HRT. The risk in current ERT/HRT users was increased to 2-3 cases per 10,000 women per year. The increased risk was found only in current ERT/HRT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. These findings were similar for commonly used transdermal and oral doses with a possible dose dependent effect on risk.

In the oestrogen-plus-progestin substudy of WHI, a statistically significant 2-fold greater rate of VTE (deep venous thrombosis [DVT] and pulmonary embolism [PE]) was reported in women receiving the oestrogen/progestin combination, compared to women receiving placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and PE (18 vs. 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted.

In the oestrogen-alone substudy of WHI, the increased risk of DVT was reported to be statistically significant (23 vs. 15 per 10,000 person-years). The risk of PE was reported to be increased, although it did not reach statistical significance. The increase in VTE (DVT and PE) risk was demonstrated during the first two years (30 vs. 22 per 10,000 women-years). Should a VTE occur or be suspected, oestrogens should be discontinued immediately.

If feasible, oestrogens should be discontinued at least four to six weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilisation.

Malignant neoplasms

Breast cancer
Studies involving the use of oestrogens by postmenopausal women have reported inconsistent results on the risk of breast cancer. The most important randomised clinical trial providing information about this issue is the Women's Health Initiative (WHI). In the oestrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer.

Some observational studies have reported an increased risk of breast cancer for oestrogen-alone therapy after several years of use. The risk increased with duration of use, and appeared to return to baseline within approximately five years after stopping treatment (only the observational studies have substantial data on risk after stopping).

The use of oestrogen has been reported to result in an increase in abnormal mammograms requiring further evaluation.

In the oestrogen-plus-progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of invasive breast cancer (RR 1.24, 95% nCI 1.01-1.54); invasive breast cancers were larger and diagnosed at a more advanced stage in the active therapy group compared to those in the placebo group. The absolute risk was 41 vs. 33 cases per 10,000 women-years, for oestrogen plus progestin compared with placebo, respectively. Metastatic disease was rare, with no apparent difference between groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between groups.

Epidemiologic studies (not necessarily including Totelle) have reported an increased risk of breast cancer in women taking oestrogens or oestrogen/progestin combinations for HRT for several years. The excess risk increases with duration of use and seems to return to baseline in the course of about five years after stopping treatment. These studies also suggest that the risk of breast cancer is greater and becomes apparent earlier with oestrogen/progestin combination therapy as compared to the use of oestrogens alone.

Studies evaluating various HRT formulations did not show significant variation in the relative risk of breast cancer among formulations regardless of the oestrogen/progestin components, doses, regimens, or route of administration.

According to data from epidemiologic studies, about 32 women in every 1,000 women who never used HRT are expected to have breast cancer diagnosed between the ages of 50 and 65 years. Among 1,000 current or recent users of oestrogen-only preparations, it is estimated that 5 and 10 years of use beginning at age 50 result in 1.5 (95% confidence interval [CI], 0-3) and 5 (95% CI, 3-7), respectively, additional breast cancers diagnosed by age 65 years. The corresponding numbers for those using oestrogen/progestin combinations are 6 (95% CI, 5-7) and 19 (95% CI, 18-20), respectively.

Use of oestrogen alone and oestrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

Endometrial cancer
The reported endometrial cancer risk among unopposed oestrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on oestrogen dose. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after ERT is discontinued.

Adding a progestin to postmenopausal oestrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

In a subset of WHI, no increased risk of endometrial cancer after an average of 5.6 years of treatment with the oestrogen/progestin combination compared to placebo was observed.

Clinical surveillance of all women taking oestrogen or oestrogen plus progestin combinations is important. Adequate diagnostic measures should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal uterine bleeding.

Ovarian cancer
In some epidemiologic studies, the use of oestrogen-plus-progestin and oestrogen-only products has been associated with an increased risk of ovarian cancer over multiple years of use. Other epidemiologic studies have not found these associations. The analysis of the WHI data suggested that oestrogen plus progestin therapy may increase the risk of ovarian cancer.

Other Conditions

Dementia
A substudy of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, reported an increased risk of developing probable dementia when compared with placebo.

Since this study was conducted in women aged 65-79 years, it is unknown whether these findings apply to younger postmenopausal women (see section 4.4).

Gallbladder disease
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving ET/HT has been reported.

Visual abnormalities
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Fluid retention
Because oestrogens/progestins may cause some degree of fluid retention, patients with conditions which might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypertriglyceridemia
Caution should be exercised in patients with pre-existing hypertriglyceridemia since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this population. Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy.

Impaired liver function
Oestrogens/progestins may be poorly metabolised in patients with impaired liver function.

History of cholestatic jaundice
For patients with a history of cholestatic jaundice associated with past oestrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

Addition of a progestin when a woman has not had a hysterectomy
Studies of the addition of a progestin for 10 or more days of a cycle of oestrogen administration or daily with oestrogen in a continuous regimen have reported a lowered incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

In a subset of WHI no increased risk of endometrial cancer after an average of 5.6 years of treatment with the oestrogen/progestin combination compared to placebo was observed. There are, however, possible risks that may be associated with the use of progestins in oestrogen replacement regimens compared to oestrogen-alone regimens. These include (a) an increased risk of breast cancer (see section 4.4); (b) adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL); and (c) impairment of glucose tolerance.

Elevated blood pressure
In a small number of case reports, substantial increases in blood pressure during ERT have been attributed to idiosyncratic reactions to oestrogens. In a large, randomised, placebo-controlled clinical trial a generalised effect of ERT on blood pressure was not seen.

Exacerbation of other conditions
Hormone replacement therapy may cause an exacerbation of asthma, epilepsy, migraine, diabetes mellitus with or without vascular involvement, porphyria, systemic lupus erythematosus, and hepatic hemangiomas, and should be used with caution in women with these conditions.

Endometriosis may be exacerbated with administration of oestrogen therapy.

Hypocalcemia
Oestrogen therapy should be used with caution in women with hypoparathyroidism, as oestrogen-induced hypocalcemia may occur.

Hypothyroidism
Oestrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women dependent on thyroid hormone replacement therapy, who are also receiving oestrogens, may require increased doses of

their thyroid-replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Uterine bleeding
Certain patients may develop abnormal uterine bleeding (see section 4.4).

Geriatric use
There have not been sufficient numbers of geriatric women involved in clinical studies utilising PREMPRO or PREMPHASE to determine whether those over 65 years of age differ from younger subjects in their response to PREMPRO or PREMPHASE.

The Women's Health Initiative Study
In the Women's Health Initiative (WHI) oestrogen plus progestin substudy (daily conjugated oestrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age.

In the WHI oestrogen-alone substudy (daily CE [0.625 mg] vs. placebo), there was a higher relative risk of stroke in women greater than 65 years of age.

The Women's Health Initiative Memory Study
In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving oestrogen plus progestin or oestrogen alone when compared to placebo. It is unknown whether this finding applies to younger postmenopausal women. Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants, anti-infectives, dexamethasone and herbal preparations containing St. John's Wort (*Hypericum perforatum*). Strong CYP3A4 inducers such as phenobarbital, phenytoin, carbamazepine, rifampicin and dexamethasone may reduce plasma concentrations of 17ß-estradiol. Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

CYP3A4 inhibitors such as cimetidine, erythromycin and ketoconazole may increase plasma concentrations of 17ß-estradiol and may result in increased risk of side effects.

In vitro studies have shown that trimegestone may inhibit cytochrome P450 2C19 (CYP2C19). The clinical relevance is not known; however trimegestone may moderately increase the plasma concentrations of drugs metabolised via CYP2C19 such as citalopram, imipramine, and diazepam. Similar *in vitro* studies with cytochrome P450 3A4 (CYP3A4), which is partially responsible for trimegestone metabolism, have demonstrated a low potential for an interaction.

4.6 Pregnancy and lactation

Totelle is not indicated during pregnancy.

If pregnancy occurs during medication with Totelle, treatment should be withdrawn immediately. For trimegestone no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see section 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

Totelle is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The adverse reactions listed in the table are based on post-marketing spontaneous (reporting rate), clinical trials and class-effects. Breast pain is a very common adverse event reported in ≥ 10% of patients.

These frequencies are based on conjugated equine estrogens plus medroxyprogesterone acetate (MPA) data.

System Organ Class	**Very common ADRs (≥ 1/10)**	**Common ADRs (≥ 1/100, < 1/10)**	**Uncommon ADRs (≥ 1/1,000, < 1/100)**	**Rare ADRs (≥ 1/10,000, < 1/1,000)**	**Very Rare ADRs (< 1/10,000), isolated reports**
Infections and infestations	None	Vaginitis	Vaginal candidiasis	None	None
Neoplasms benign and malignant (including cysts and polyps)	None	None	None	Breast cancer, Fibrocystic breast changes, Ovarian cancer, Growth potentiation of benign meningioma	Endometrial cancer, Enlargement of hepatic hemangiomas
Immune system disorders	None	None	None	Anaphylactic/ anaphylactoid reactions, including urticaria and angioedema	None
Metabolism and nutrition disorders	None	None	None	Glucose intolerance	Exacerbation of porphyria, Hypocalcemia
Psychiatric disorders	None	Depression	Changes in libido, Mood disturbances, Dementia	Irritability	None
Nervous system disorders	None	None	Dizziness, Headache, Migraine, Anxiety	Stroke, Exacerbation of epilepsy	Exacerbation of chorea
Eye disorders	None	None	Intolerance to contact lenses	None	Retinal vascular thrombosis
Cardiac disorders	None	None	None	Myocardial infarction	None
Vascular disorders	None	None	Venous thrombosis, Pulmonary embolism	Superficial thrombophlebitis	None
Respiratory, thoracic and mediastinal disorders	None	None	None	Exacerbation of asthma	None
Gastrointestinal disorders	None	None	Nausea, Bloating, Abdominal pain	Vomiting, Pancreatitis, Ischaemic colitis	None

System Organ Class	Very common ADRs (≥ 1/10)	Common ADRs (≥ 1/100, < 1/10)	Uncommon ADRs (≥ 1/1,000, < 1/100)	Rare ADRs (≥ 1/10,000, < 1/1,000)	Very Rare ADRs (< 1/10,000), isolated reports
Hepatobiliary disorders	None	None	Gallbladder disease	None	Cholestatic jaundice
Skin and subcutaneous tissue disorders	None	None	Alopecia, Acne, Pruritus	Chloasma/melasma, Hirsutism, Rash	Erythema multiforme, Erythema nodosum
Musculoskeletal, connective tissue disorders	None	Arthralgias, Leg cramps	None	None	None
Reproductive system and breast disorders	Breast pain	Breakthrough bleeding/spotting, Dysmenorrhea, Breast tenderness/enlargement/ discharge	Change in menstrual flow, Change in cervical ectropion and secretion	Galactorrhoea, Increased size of uterine leiomyomata	Endometrial hyperplasia
General disorders and administration site conditions	None	None	Oedema	None	None
Investigations	None	Changes in weight (increase or decrease), Increased triglycerides	None	None	Increase in blood pressure

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 1,000 never-users of HRT over a 5-year period[*2]	Risk ratio& 95% CI[#]	Additional cases per 1,000 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.
[*2]*Taken from baseline incidence rates in developed countries*

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

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1,000 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	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.			
[*3]*WHI study in women with no uterus, which did not show an increase in risk of breast cancer*			

Endometrial cancer risk

Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1,000 women with an intact uterus not using HRT.

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 1,000 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 2,500 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 1,000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1,000 HRT users
Oral oestrogen-only[*4]			
50-59	7	1.2 (0.6-2.4)	1 (-3 - 10)
Oral combined oestrogen-progesten			
50-59	4	2.3 (1.2-4.3)	5 (1 – 13)
[*4]*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-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen plus 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 & 95% CI**	**Additional cases per 1000 HRT users over 5 years**
50-59	8	1.3 (1.1-1.6)	3 (1-5)
[*5]*No differentiation was made between ischaemic and haemorrhagic stroke.*			

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:
- 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 sections 4.3 and 4.4.
- Skin and subcutaneous tissue disorders: vascular purpura.

Paediatric population
Clinical studies have not been conducted in the paediatric population.

4.9 Overdose

Symptoms of overdosage of oestrogen-containing products in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment if necessary should be symptomatic.