PRODUCT INFORMATION

KLIOGEST®

WARNING

Estrogens and progestagens should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo. (See 'Clinical Trials'and 'Precautions.')

The WHI study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated estrogens (0.625 mg) relative to placebo. (See 'Clinical Trials'and 'Precautions.')

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 to 5.2 years of treatment with conjugated estrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See 'Clinical Trials'and 'Precautions.')

Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestagens were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestagens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

NAME OF THE MEDICINE

Estradiol (as hemihydrate)
Norethisterone acetate

DESCRIPTION

Kliogest is a continuous combined estrogen/progestagen hormone replacement therapy (HRT) preparation comprising 28 tablets. Each tablet contains 2 mg 17β-estradiol and 1 mg norethisterone acetate. The estrogen component of Kliogest substitutes for the loss of endogenous estrogen production in postmenopausal women. The progestagen component protects the endometrium from estrogen-induced hyperstimulation. This regimen is intended to avoid monthly withdrawal bleeding.

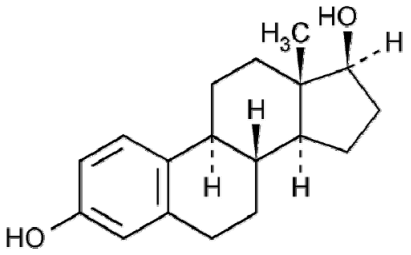
Active ingredients

Estradiol - chemical name: estra-1,3,5(10)-triene-3,17β-diol (as hemihydrate). Estradiol is a white or almost white crystalline powder which is practically insoluble in water and soluble in acetone. Estradiol has 5 chiral centres. The molecular formula is $C_{18}H_{24}O_2$. Estradiol hemihydrate has a molecular weight of 281.39.

Norethisterone acetate - chemical name: 17β-acetoxy-19-nor-17α-pregn-4-en-20-yn-3-one. Norethisterone acetate (NETA) is a white or yellowish-white crystalline powder which is practically insoluble in water and soluble in ethanol and acetone. Norethisterone acetate has 6 chiral centres. The molecular formula is $C_{22}H_{28}O_3$, with a molecular weight of 340.5.

Structure

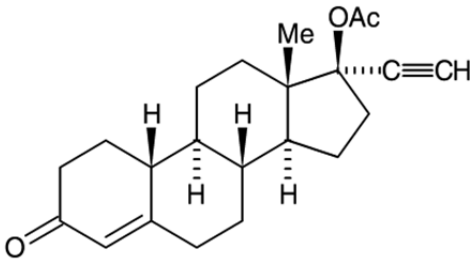
Estradiol hemihydrate



'½H_2O'

CAS no.: 35380-71-3

Norethisterone acetate



CAS no. 51-98-9

Excipients

The tablet cores contain lactose, maize starch, hyprolose, talc and magnesium stearate. The film coating contains hypromellose, triacetin and talc. Kliogest does not contain clinically significant amounts of gluten.

PHARMACOLOGY

Pharmacokinetics

Micronised estradiol is rapidly and efficiently absorbed from the gastrointestinal tract following oral administration. Peak plasma concentrations of estradiol occur 4-6 hours after tablet ingestion. Thereafter elimination is slow and estradiol levels are maintained above baseline for 24 hours. The steady state plasma level of estradiol ranges between 70-100 pg/mL. Estradiol has a mean half-life of approximately 14 hours. In the bloodstream more than 90% of estradiol is bound to plasma proteins. Some estradiol is converted to oestrone in the intestinal mucosa before absorption into the portal vein. During passage through the liver a significant proportion of estradiol is metabolised to oestrone. Oestriol and hydroxyoestrones are also produced as well as sulfate and glucuronate conjugates. Circulating oestrone sulfate may be reconverted to oestrone and estradiol in extrahepatic organs like the uterus. Estrogens are excreted into the bile and undergo significant enterohepatic cycling. Biologically inactive glucuronide and sulfate conjugates are excreted in the urine (90 to 95%) and unconjugated estrogen metabolites appear in the faeces (5 to 10%). Estrogens are also secreted in the milk of nursing mothers.

Norethisterone acetate is rapidly absorbed and transformed to norethisterone, then metabolised and excreted as glucuronide and sulfate conjugates. About half the dose is recovered in the urine within 24 hours, the remainder being reduced to less than 1% of the dose within 5 to 6 days. Peak plasma concentrations of norethisterone occur 1 to 2 hours after tablet ingestion. The terminal plasma half life is about 10 hours. Norethisterone concentrations return to basal levels within 24 hours.

Pharmacodynamics

The pharmacological actions of exogenous estradiol are similar to the physiological effects of the endogenous hormone. The 17β-estradiol in Kliogest is chemically and biologically identical to endogenous human estradiol and is therefore classified as a human estrogen.

Norethisterone acetate given orally has progestational actions similar to those of progesterone and, in addition, has weak estrogenic and androgenic properties.

Kliogest restores plasma estrogen levels and thus relieves or decreases estrogen deficiency symptoms. Kliogest suppresses gonadotrophin secretion (FSH/LH) and improves vaginal cytology in post-menopausal women without adversely affecting the serum lipid/lipoprotein or haemostatic profiles. It is effective in preventing estrogen-induced hyperplasia of the endometrium. The endometrial findings with Kliogest have been mainly atrophic or in some cases secretory or weakly proliferative; all of which can be considered normal endometrial states. Amenorrhoea or oligomenorrhoea is achieved in most women after 3 to 6 months' of Kliogest treatment.

When Kliogest is used for the short term relief of menopausal symptoms, it will provide a concomitant preventive effect in reducing bone mineral density loss and fracture risk. The long-term prevention of bone mineral density loss should be restricted to women at risk of developing osteoporotic fractures. Factors that predispose to postmenopausal osteoporosis include: low bone mass; early menopause; family history of osteoporosis; white or Asian race; thin, small frame; inadequate calcium nutrition; cigarette smoking; alcohol abuse; sedentary lifestyle; recent prolonged systemic corticosteroid use.

There is no evidence of a minimum duration of hormone replacement therapy (HRT) which will be of benefit in reducing the risk of osteoporotic fractures in women at the age of peak fracture incidence (75 years and over).

CLINICAL TRIALS

Women's Health Initiative (WHI) Studies

A substudy of the Women's Health Initiative (WHI) enrolled 16,608 predominantly healthy postmenopausal women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic) to assess the risks and benefits of the use of a continuous combined regimen of conjugated estrogens (CE) 0.625 mg/day plus medroxyprogesterone acetate (MPA) 2.5 mg/day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE + MPA on menopausal symptoms. The estrogen plus progestagen substudy was

stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results are presented in Table 1.

Table 1

Relative and absolute risk seen in the estrogen plus progestagen substudy of WHI[a]

Event[c]	Relative Risk CE+MPA vs. Placebo at 5.2 Years (Nominal 95% CI*)	Placebo n = 8102	CE+MPA n = 8506
		Absolute Risk per 10,000 Women-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index[c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis[d]	2.07 (1.49-2.87)	13	26
Vertebral fractures[d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures[d]	0.77 (0.69-0.86)	170	131

a: adapted from JAMA, 2002; 288:321-333
b: includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
c: a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
d: not included in Global Index
*: nominal confidence intervals unadjusted for multiple looks and multiple comparisons. Except for deep vein thrombosis and other osteoporotic fractures, based on adjusted confidence intervals, the relative risks were not statistically significant.

For those outcomes included in the "global index", the absolute excess risks per 10,000 women-years in the group treated with CE + MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See 'Warning' and 'Precautions.')

Women's Health Initiative Memory Study (WHIMS)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE + MPA on the incidence of probable dementia (primary outcome) compared with placebo.
After an average follow-up of 4 years, 40 women in the estrogen/progestagen group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05

(95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See 'Warning' and 'Precautions' ('Dementia' and 'Use in the elderly.'))

INDICATIONS

1. Short term symptomatic treatment of postmenopausal estrogen deficiency (see 'Dosage and Administration' and 'Clinical Trials').

2. For the prevention of postmenopausal bone mineral density loss.

   When prescribed solely for the prevention of postmenopausal bone mineral density loss, therapy should only be prescribed for women who are at high risk of osteoporosis and future fracture and who are intolerant of, or contraindicated for, non-estrogen products approved for prevention of osteoporosis. Life style modifications and the risk benefit profile of Kliogest should be taken into careful consideration and discussed with the patient, to allow the patient to make an informed decision prior to prescribing. See 'Precautions' and 'Dosage and Administration'.

Kliogest is for use in postmenopausal women with an intact uterus. In perimenopausal women treated with Kliogest the incidence of vaginal bleeding is unacceptably high and therefore therapy should not be initiated sooner than one year after the last menstrual period.

CONTRAINDICATIONS

- Known, suspected, or past history of breast cancer
- Known, suspected or past history of estrogen-dependent neoplasia e.g. endometrial cancer.
- Untreated endometrial hyperplasia
- Genital bleeding of unknown aetiology
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism), or active thrombophlebitis.
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency (see 'Precautions')
- Active or previous 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 ingredients or any of the excipients
- Porphyria
- Known or suspected pregnancy

PRECAUTIONS

The benefits and risks of estrogen / progestagen therapy must always be carefully weighed, including consideration of the emergence of risks as therapy continues. A careful appraisal of the risks and benefits should be undertaken at least annually.

Kliogest has no contraceptive effect.

Kliogest tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

The toxicity profiles of estradiol and norethisterone acetate are well known. There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Product Information.

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examinations 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 (please see the "Breast Cancer" section 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 Kliogest, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for, thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumours e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma, hepatic haemangioma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosis
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis.

Estrogens may be poorly metabolised in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

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

Malignant neoplasms

Endometrial hyperplasia and carcinoma
Treatment with unopposed estrogens increases the risk of endometrial carcinoma. The appropriate addition of a progestagen to an estrogen regimen lowers this additional risk. Endometrial hyperplasia (atypical or adenomatous) often precedes endometrial cancer. Studies with Kliogest show that the continuous administration of a progestagen during the entire estrogen treatment period reduces the risk of endometrial hyperplasia.

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose (see 'Adverse Effects'). Most studies show no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestagen combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1% or less with CE + MPA in two large clinical trials. In the two large clinical trials described above, two cases of endometrial cancer were reported to occur among women taking the estrogen/progestagen combination therapy.

Breast cancer
The use of estrogens and progestagens by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomised clinical trial providing information about this issue is the Women's Health Initiative (WHI) trial of estrogen plus progestagen (see 'Clinical Trials.) The results from observational studies are generally consistent with those of the WHI clinical trial.

After a mean follow-up of 5.6 years, the WHI trial reported an increased risk of breast cancer in women who took estrogen plus progestagen. Observational studies have also reported an increased risk for estrogen/progestagen combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestagen combination therapy as compared to estrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen/progestagen combinations, doses, or routes of administration.

In the WHI trial of estrogen plus progestagen, 26% of the women reported prior use of estrogen alone and/or estrogen/progestagen combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for estrogen plus progestagen compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for estrogen plus progestagen compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for estrogen plus progestagen compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen plus progestagen group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of estrogens alone or estrogens plus progestagens compared to never users, while the estrogen plus progestagen substudy of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results. The use of estrogen plus progestagen has been reported to result in an increase in abnormal mammograms requiring further evaluation. Mammographic density may be increased after the use of combined HRT. This may have implications for the sensitivity and specificity of breast cancer screening.

Breast status should also be closely monitored in women with a history of or known breast nodules, fibrocystic disease, or with a family history of breast cancer

Although obese women are at an increased risk of having breast cancer, HT did not further increase this risk.

Combination HRT should not be used in hysterectomised women because it is not needed in these women and it may increase the risk of breast cancer.

Ovarian cancer
Ovarian cancer is much rarer than breast cancer.

The estrogen plus progestagen substudy of WHI reported that, after an average follow-up of 5.6 years, the relative risk of ovarian cancer for estrogen plus progestagen versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant. The absolute risk for estrogen plus progestagen versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-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 ‘Adverse Effects’).

Cardiovascular disorders

Estrogen/progestagen therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogen/progestagen therapy should be discontinued immediately (see 'Contraindications.')

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolaemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, use of estrogens, older age, major surgery, prolonged immobilisation, obesity, pregnancy/postpartum period, cancer and systemic lupus erythematosus) should be managed appropriately.

Coronary heart disease and stroke
In the estrogen plus progestagen substudy of the Women's Health Initiative (WHI) study, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE + MPA compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted. (See 'Clinical Trials.')

In the same substudy of WHI, an increased risk of stroke was observed in women receiving estrogen/progestagen compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

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 CE + MPA demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE + MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the estrogen/progestagen-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial 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 estrogen/progestagen-treated group and the placebo group in HERS, HERS II, and overall.

Venous thromboembolism (VTE)
In the estrogen plus progestagen substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE + MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the estrogen/progestagen-treated group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See 'Clinical Trials.')

HRT is associated with a 1.3- to 3-fold risk of developing 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 'Adverse Effects').

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 'Contraindications').

Generally recognised risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m²), 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. HRT should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilisation. 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 venous thromboembolism at a 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 using 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).

Dementia

HRT use does not improve cognitive function In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 women aged 65 to 79 years was randomised to CE + MPA or placebo. A population of 2,947 hysterectomised women, aged 65 to 79 years, was randomised to CE alone or placebo. In the planned analysis, pooling the events in women receiving CE alone or CE + MPA in comparison to those in women on placebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60). In the estrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. In the estrogen plus progestagen group, after an average follow-up of 4 years, a RR of 2.05 (95% CI 1.21-3.48) for probable dementia was observed compared to placebo. Since this study was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See 'Precautions' – 'Use in the elderly.')

Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Hypercalcaemia

Estrogen administration may lead to severe hypercalcaemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

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 or diplopia. If examination reveals papilloedema or retinal vascular lesions, estrogens should be discontinued.

General precautions

Addition of a progestagen when a woman has not had a hysterectomy.

Studies of the addition of a progestagen for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestagens with estrogens compared with estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance.

Hypertriglyceridaemia

In patients with pre-existing hypertriglyceridaemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid retention

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

Hypocalcaemia

Estrogens should be used with caution in individuals with severe hypocalcaemia.

Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of estrogen therapy.

Angioedema
Estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

Carcinogenicity

Supra-physiological doses of estradiol have been associated with the induction of tumours in estrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established. See 'Precautions'- 'Malignant neoplasms.'

Genotoxicity

There is limited evidence available in the literature suggesting that estradiol may be weakly genotoxic at high doses. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy in mammalian cells, and two groups reported an increase in the incidence of sister chromatid exchanges, indicative of DNA damage. Neither of these latter effects were induced by estradiol in human lymphocyte cultures. Importantly, there was no evidence for increased micronuclei formation in well controlled rodent bone marrow assays.

Use in the elderly

The experience of treating women older than 65 years' is limited. Pharmacokinetics in the elderly have not been studied.

Of the total number of subjects in the estrogen plus progestagen substudy of the Women's Health Initiative study, 44% (n = 7320) were 65 years and over, while 6.6% (n = 1,095) were 75 years and over (see 'Clinical Trials'). There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age.

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 women aged 65 to 79 years was randomised to a continuous combined regimen of conjugated estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day or placebo. A population of 2,947 hysterectomised women, aged 65 to 79 years, was randomised to conjugated estrogens (CE 0.625 mg) or placebo. In the planned analysis, pooling the events in women receiving CE or CE + MPA in comparison to those in women on placebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60). In the estrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. In the estrogen plus progestagen group, after an average follow-up of 4 years, a RR of 2.05 (95% CI 1.21-3.48) for probable dementia was observed compared to placebo. Since this study was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See 'Precautions'-'Dementia.')

With respect to efficacy in the approved indications, there have not been sufficient numbers of geriatric patients involved in studies utilising estrogens and progestagens to determine whether those over 65 years of age differ from younger subjects in their response to estrogens and progestagens.

Use in pregnancy
Category D. Known or suspected pregnancy is a contraindication to Kliogest therapy.

In animal studies, maternal administration of high doses of estrogens has produced urogenital malformations in the offspring. The relevance of these animal findings for the clinical use of estradiol is uncertain, but is considered likely to be low. Animal studies have also shown that high doses of progestagens can cause masculinisation of the female foetus.

Clinically, data on a limited number of pregnancies indicate adverse effects of norethisterone on the fetus. At doses higher than normally used in OC and HRT formulations, masculinisation of female fetuses was observed.

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of estrogens and progestagens indicate no teratogenic or fetotoxic effect.

Use in lactation

Kliogest is not indicated during lactation.

INTERACTIONS WITH OTHER MEDICINES

The metabolism of estrogens and progestagens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as barbiturates (e.g. phenobarbital), anticonvulsants (e.g. phenytoin, carbamazepin), antihistamines, phenylbutazone and some anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz, telaprevir). Ritonavir, telaprevir 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 estrogens and progestagens.

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

Drugs that inhibit the activity of hepatic microsomal drug metabolising enzymes eg: ketoconazole, may increase circulating levels of the active substances in Kliogest.

Estrogens can also affect the actions of other drugs eg anticoagulants, antidiabetic agents, antifibrinolytic agents, pethidine, drugs which decrease serum folate, imipramine, thyroid hormones and corticosteroids.

Oral contraceptives (OC) containing ethinylestradiol have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered. Similar interaction may exist between HRT containing estradiol and lamotrigine. Therefore, dosage adjustment of lamotrigine may be necessary for seizure control.Concomitant administration of cyclosporin may cause increased blood levels of cyclosporin, creatinine and transaminases due to decreased metabolism of cyclosporin in the liver.

Some laboratory tests may be influenced by estrogen therapy, such as tests for glucose tolerance or thyroid function

ADVERSE EFFECTS

Clinical experience

The most frequently reported adverse events in the clinical trials with Kliogest were vaginal bleeding and breast pain/tenderness, reported in approximately 10% to 30% of patients. Vaginal bleeding usually occurred in the first months of treatment. Breast pain usually disappeared after a few months of therapy. Adverse reactions observed with a higher frequency in patients treated with Kliogest as compared to placebo, and which on an overall judgement are considered possibly or probably related to treatment, are presented below. See also 'Clinical Trials' and 'Precautions.'

Table 2

System organ class	**Very common ≥1/10**	**Common ≥1/100; <1/10**	**Uncommon ≥1/1,000; <1/100**	**Rare ≥1/10,000; <1/1,000**
Infections and infestations		Genital candidiasis or vaginitis. See also *Reproductive system and breast disorders.*		
Immune system disorders			Hypersensitivity. See also *Skin and subcutaneous tissue disorders.*	
Metabolism and nutrition disorders		Fluid retention. See also *General disorders and administration site conditions.*		
Psychiatric disorders		Depression or depression aggravated.	Nervousness	
Nervous system disorders		Headache, migraine or migraine aggravated.		
Vascular disorders			Thrombophlebitis superficial.	Pulmonary embolism Thrombophlebitis deep Venous thrombosis
Gastrointestinal disorders		Nausea Abdominal pain Abdominal distension Abdominal discomfort	Flatulence or bloating	Cholelithiasis
Skin and subcutaneous tissue disorders			Pruritis or urticaria Alopecia, hirsutism or acne Skin reactions	
Musculoskeletal, connective tissue and bone disorders		Back pain Leg cramps		
Reproductive system and breast disorders	Breast pain or breast tenderness	Breast enlargement or breast oedema Uterine fibroids		

System organ class	Very common ≥1/10	Common ≥1/100; <1/10	Uncommon ≥1/1,000; <1/100	Rare ≥1/10,000; <1/1,000
	Vaginal haemorr-hage	aggravated or uterine fibroids recurrence or uterine fibroids		
General disorders and administration site conditions		Oedema peripheral	Drug ineffective	
Investigations		Weight increased		
Respiratory, thoracic and mediastinal disorders				Asthma

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

Post-marketing experience

In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported, and are by an overall judgement considered possibly related to treatment with Kliogest. The reporting rate of these spontaneous adverse drug reactions is very rare (<1/10,000, not known (cannot be estimated from the available data)). Post-marketing experience is subject to underreporting especially with regard to trivial and well known adverse drug reactions. The presented frequencies should be interpreted in that light:

- Neoplasms benign and malignant (including cysts and polyps): Endometrial cancer
- Immune system disorders: generalised hypersensitivity reactions (e.g. anaphylactic reaction/shock)
- Psychiatric disorders: Insomnia, anxiety, libido decreased, libido increased
- Nervous system disorders: Dizziness, stroke
- Eye disorders: Visual disturbances
- Vascular disorders: Hypertension aggravated
- Cardiac disorders: myocardial infarction
- Gastrointestinal disorders: Dyspepsia, vomiting
- Hepatobiliary disorders: Gallbladder disease, cholelithiasis, cholelithiasis aggravated, cholelithiasis recurrence
- Skin and subcutaneous tissue disorders: Seborrhoea, rash, angioneurotic oedema
- Reproductive system and breast disorders: Endometrial hyperplasia, vulvovaginal pruritus

- Investigations: Weight decreased, blood pressure increased

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

- Skin and subcutaneous disorders: alopecia, chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia (see 'Precautions')
- Gastrointestinal disorders: Crohn's disease, ulcerative colitis
- Dry eyes
- Tear film composition changes

Breast cancer risk
An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestagen therapy for more than 5 years. Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen-progestagen combinations. The level of risk is dependent on the duration of use (see 'Precautions.')

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)	**Incidence per 1000 never-users of HRT over 5 years***	**Risk ratio****	**Additional cases per 1000 HRT users over 5 years' use (95% CI)**
Estrogen-only HRT			
50 – 65	9 – 12	1.2	1 - 2 (0 - 3)
Combined estrogen-progestagen			
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 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.			

US WHI studies – Additional risk of breast cancer after 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' use (95% CI)**
CEE estrogen-only			
50 – 79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0) *
CEE+MPA estrogen-progestagen**			
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 in non-users.			

Ovarian cancer
Use of estrogen-only or combined estrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see 'Precautions.') 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 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism
HRT is associated with a 1.3- to 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 HRT (see 'Precautions'). Results of the WHI studies are presented below:

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 over 5 years' use (95% CI)**
Oral estrogen-only*			
50 - 59	7	1.2 (0.6 - 2.4)	1 (-3 – 10)
Oral combined estrogen-progestagen			
50 - 59	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 estrogen-progestagen HRT over the age of 60 (see 'Precautions').

Risk of ischaemic stroke
The use of estrogen-only and estrogen-progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. 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 'Precautions').

WHI studies combined – Additional risk of ischaemic stroke* 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' use (95% CI)**
50 - 59	8	1.3 (1.1 – 1.6)	3 (1 – 5)

*No differentiation was made between ischaemic and haemorrhagic stroke

DOSAGE AND ADMINISTRATION

Kliogest is a continuous-combined HRT product intended for use in women with an intact uterus. Kliogest is administered orally, without chewing, one tablet daily without interruption preferably at the same time each day.

In women not previously treated with HRT, Kliogest may be started on any convenient day. In women in transition from sequential HRT, treatment should be started at the end of the scheduled bleed.

If symptoms such as hot flushes have ceased, consideration of transferring to local vaginal treatment should be given if troublesome local symptoms remain.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and, when indicated, pharmacological therapy. Postmenopausal women require an adequate daily intake of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with sub-optimal dietary intake. Vitamin D supplementation may also be required to ensure adequate daily intake in postmenopausal women.

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next twelve hours. If more than 12 hours have passed the tablet should be discarded. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

Duration of therapy

HRT should be prescribed at the lowest effective dose and for shortest duration. The continuation of the treatment should be re-evaluated annually. Women who have undergone a premature menopause may require longer term treatment.

OVERDOSAGE

Overdosage may cause nausea and vomiting. There is no specific antidote and treatment should be symptomatic.

PRESENTATION AND STORAGE CONDITIONS

Kliogest is supplied in a calendar pack containing 28 white, biconvex, film-coated tablets marked NOVO 281 on one side , blank on the other side, with a diameter of 6mm. Each tablet contains 2 mg estradiol (as hemihydrate) and 1 mg norethisterone acetate.

Use of the calendar pack

The first tablet to be taken is under the sealed opening in the transparent outer rim of the pack. Turn the inner disc of the pack until the day of the week on which the first tablet is to be taken is opposite the sealed opening. Lift off the plastic seal with a finger-nail and remove the first tablet from the pack. Each day, turn the transparent outer rim of the pack in the direction of the arrow to obtain the next tablet. Continue until all tablets have been taken.

Store Kliogest in a dry place, protected from light. Keep the container in the outer carton in order to protect it from light. Store below 25°C. Do not refrigerate. Keep out of reach of children.

NAME AND ADDRESS OF THE SPONSOR

Novo Nordisk Pharmaceuticals Pty Ltd
Level 3
21 Solent Circuit
Baulkham Hills NSW 2153

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

17 June 2011

DATE OF MOST RECENT AMENDMENT

1 December 2016