

New Zealand Datasheet

1 PRODUCT NAME

KLIOVANCE®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

17 β -oestradiol 1mg and Norethisterone acetate 0.5mg tablets.

3 PHARMACEUTICAL FORM

Kliovance calendar dial pack contains 28 tablets as described below:

White, round, film coated, biconvex tablets with a diameter of 6mm. The tablets are engraved "NOVO 288" on one side and the Apis bull on the other side. Each tablet contains 1mg of 17 β -oestradiol and 0.5mg of norethisterone acetate.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Kliovance is indicated for the treatment of menopausal symptoms related to oestrogen deficiency, including urogenital atrophy. Kliovance is also indicated for the prevention of osteoporosis in postmenopausal women.

The experience of treating women older than 65 years is limited.

4.2 Dose and method of administration

Kliovance is a continuous combined HRT product intended for use in women with an intact uterus. One tablet should be taken orally once a day without interruption, preferably at the same time of the day.

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.

Kliovance avoids monthly withdrawal bleeding associated with sequential hormone replacement therapy (HRT) regimens. During the initial months of therapy sporadic bleeding or spotting episodes may occur; however, these tend to decrease with time and after 9 to 12 months of treatment less than 3% of women report bleeding.

Relief of menopausal symptoms is achieved during the first few weeks of treatment in the majority of women. A switch to a higher dose combination product could be indicated if the response after 3 months is insufficient for symptom relief.

In women with amenorrhoea and not taking HRT or women in transition from another continuous combined HRT product, treatment with Kliovance may be started on any convenient day. In women in transition from a sequential HRT regimens, treatment should start right after their withdrawal bleeding has ended.

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next 12 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.

4.3 Contraindications

- Known hypersensitivity to the active substances or the excipients
- Known, past or suspected breast cancer
- Known, past or suspected oestrogen dependent neoplasia e.g. endometrial cancer

- Porphyria
- 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 previous arterial thromboembolic diseases (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

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. The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. All prospective and current users should be informed of these risks and benefits. The need for treatment with HRT should be reviewed on a yearly basis and include a physical and gynaecological examination. HRT should be used only in women with menopausal symptoms and ordinarily not for the long term maintenance of general health as the risks of long term treatment with HRT in most circumstances outweigh the benefits. HRT should be prescribed at the lowest effective doses and for the shortest duration (generally not longer than 3-4 years), consistent with the treatment goals and risks for the individual women.

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

Medical examination/follow-up

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

In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment, the risk may remain elevated for more than 10 years.

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

Close clinical surveillance of all women taking oestrogens 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" oestrogens results in a different endometrial risk profile than synthetic oestrogens of equivalent oestrogen dose.

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

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

The excess risk becomes apparent within a few years of use, but returns to baseline within a few (at most 5) 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 to 3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8).

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

Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery prolonged immobilisation, obesity (BMI > 30 kg/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. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at 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 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)

For the WHI study, a global index summarising the balance of risks and benefits included an analysis of the 2 primary outcomes, invasive breast cancer and CHD, and the following secondary outcomes: stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. The women enrolled in the study had a mean age at entry of 63.3 years. On average they were overweight (mean body mass index [BMI] = 28.5) and one-third were obese (BMI ≥ 30), 50% were previous or current smokers, one-third had received treatment for high blood pressure and over 10% had raised cholesterol levels requiring medication.

The oestrogen plus progestagen arm of the WHI study was prematurely stopped after an average follow-up of 5.2 years, based on the finding of increased breast cancer risk. The study also found increases in coronary heart disease, stroke, and pulmonary embolism in study participants on oestrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of oestrogen plus progestagen, including fewer cases of hip

fractures and colon cancer, but on balance the harm was greater than the benefit (NHLBI press release July 9 2002).

Table 1: Increased Risks

	Relative Risk (RR)	Placebo arm: Cases/10000	CEE + MPA arm: Cases/10000	Increased Absolute Risk per 10000 women / year
Breast Cancer	1.26	30	38	8
Stroke	1.41	21	29	8
CHD	1.29	30	37	7
Thromboembolic Events (blood clots in legs and lungs)	2.11	16	34	18

Table 2: Decreased Risks

	Relative Risk (RR)	Placebo arm: Cases/10000	CEE + MPA arm: Cases/10000	Decreased Absolute Risk per 10000 women / year
Colorectal Cancer	0.63	16	10	6
Hip Fractures	0.66	15	10	5
Total Fractures	0.76	191	147	44

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.

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

Ischaemic stroke

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

Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

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

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

proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin and ceruloplasmin).

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

Kliovance 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.

4.5 Interaction with other medicines and other forms of interaction

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

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 oestrogens and progestagens.

Clinically, an increased metabolism of oestrogens 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 e.g. ketoconazole, may increase circulating levels of the active substances in Kliovance.

Concomitant administration of cyclosporine and Kliovance may cause increased blood levels of cyclosporine, creatinine and transaminases due to decreased metabolism of cyclosporine in the liver.

4.6 Fertility, pregnancy and lactation

Fertility

No data available

Use in Pregnancy

Known or suspected pregnancy is a contraindication of Kliovance therapy. If pregnancy occurs during medication with Kliovance, treatment should be withdrawn immediately.

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

The results of most epidemiological studies to date, relevant to inadvertent foetal exposure to combinations of oestrogens and progestagens, indicate no teratogenic or foetotoxic effect.

Use in Lactation

Kliovance is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Kliovance has no known effects on the ability to drive or use machines.

4.8 Undesirable effects

Clinical experience:

The most frequently reported adverse events in the clinical trials with Kliovance were vaginal bleeding and breast pain/tenderness, reported in approximately 10% to 20% of patients. Vaginal bleeding usually occurred in the first months of treatment. Breast pain usually disappeared after a few months of therapy. All adverse events observed in the randomised clinical trials with a higher frequency in patients treated with Kliovance or similar HRT products as compared to placebo and which on an overall judgement are possibly related to treatment are presented in the table below.

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			Thrombo-phlebitis superficial	Pulmonary embolism Deep vein thrombo-embolism
Gastrointestinal disorders		Nausea	Abdominal pain, abdominal distension or abdominal discomfort Flatulence or bloating	
Skin and subcutaneous tissue disorders			Alopecia, hirsutism or acne Pruritus or urticaria	
Musculoskeletal and connective tissue disorders		Back pain	Leg cramps	

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
Reproductive system and breast disorders	Breast pain or breast tenderness Vaginal haemorrhage	Breast oedema or breast enlargement Uterine fibroids aggravated or uterine fibroids re-occurrence or uterine fibroids		
General disorders and administration site conditions		Oedema peripheral	Drug ineffective	
Investigations		Weight increased		

Post-marketing experience:

In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported, and are by an overall judgment considered possibly related to Kliovance treatment. 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 disorder: 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 disorder: Seborrhoea, rash, angioneurotic oedema

Reproductive system and breast disorders: Endometrial hyperplasia, vulvovaginal pruritus

Investigations: Weight decreased, blood pressure increased

The following adverse reactions have been reported in association with other oestrogen/progestagen treatment:

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

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 below.

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

Age range (years)	Incidence per 1,000 never-users of HRT over 5 years *	Risk ratio**	Additional cases per 1,000 HRT users over 5 years' use (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)
* 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 1,000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 HRT users over 5 years use (95% CI)
CEE oestrogen-only			
50-79	21	0.8 (0.7-1.0)	-4 (-6-0)*
CEE+MPA oestrogen-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.			

Endometrial cancer risk

The endometrial cancer risk is about 5 in every 1,000 women with a 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 epidemiological 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 5 years of combined (sequential or continuous) HRT did not increase the risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer risk

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 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 section 4.4). Results of the WHI studies are presented below.

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 and 95% CI	Additional cases per 1,000 HRT users over 5 years' use (95% CI)
Oral oestrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)
Oral combined oestrogen-progestagen			
50-59	4	2.3 (1.2-4.3)	5 (1-13)

* 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-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 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 1,000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 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.

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 at <https://nzphvc.otago.ac.nz/reporting>.

4.9 Overdose

Symptoms

Nausea and vomiting.

Treatment

There is no specific antidote and treatment should be symptomatic. For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestagens and oestrogens, fixed combination, ATC code G03F A01

Oestrogen and progestagen for continuous combined hormone replacement therapy (HRT).

Oestradiol: The active ingredient, synthetic 17 β -oestradiol, is chemically and biologically identical to endogenous human oestradiol. It substitutes for the loss of oestrogen production in postmenopausal women, and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy.

Norethisterone acetate: Synthetic progestagen with actions similar to those of progesterone, a natural female sex hormone. As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Relief of menopausal symptoms is achieved during the first few weeks of treatment.

Kliovance is a continuous combined HRT given with the intent of avoiding the regular withdrawal bleeding associated with cyclic or sequential HRT. Amenorrhoea (no bleeding and spotting) was seen in 90% of the women during months 9-12 of treatment. Bleeding and/or spotting was observed in 27% of the women during the first 3 months of treatment and in 10% during months 10-12 of treatment.

Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued.

After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestagen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

The effect of oestrogen on bone mineral density is dose dependent and therefore, the effect

of Kliovance may be less than observed with higher doses of estradiol. The effects of Kliovance on bone mineral density were examined in 2 two year, randomised, double-blind, placebo-controlled clinical trials in postmenopausal women (n=327 in one trial, including 47 on Kliovance and 48 on Kliogest (2 mg estradiol and 1 mg norethisterone acetate); and n=135 in the other trial, including 46 on Kliovance). All women received calcium supplementation ranging from 500 to 1,000 mg daily. Kliovance significantly prevented bone loss at the lumbar spine, total hip, distal radius and total body in comparison with calcium supplemented placebo-treated women. In early postmenopausal women (1 to 5 years since last menses), the percentage change from baseline in bone mineral density at lumbar spine, femoral neck and femoral trochanter in patients completing 2 years of treatment with Kliovance was $4.8 \pm 0.6\%$, $1.6 \pm 0.7\%$ and $4.3 \pm 0.7\%$ (mean \pm SEM), respectively, while with the higher dose combination containing 2 mg E2 and 1 mg NETA (Kliogest) it was $5.4 \pm 0.7\%$, $2.9 \pm 0.8\%$ and $5.0 \pm 0.9\%$, respectively. The percentage of women who maintained or gained bone mineral density during treatment with Kliovance and Kliogest was 87% and 91%, respectively, after 2 years of treatment. In a study conducted in postmenopausal women with a mean age of 58 years, treatment with Kliovance for 2 years increased the bone mineral density at lumbar spine by $5.9 \pm 0.9\%$, at total hip by $4.2 \pm 1.0\%$, at distal radius by $2.1 \pm 0.6\%$, and at total body by $3.7 \pm 0.6\%$. In these women, Kliovance decreased bone resorption and bone formation markers to mean values within the premenopausal range.

5.2 Pharmacokinetic properties

Absorption and distribution of 17 β -estradiol

Following oral administration of 17 β -oestradiol in micronised form, rapid absorption from the gastrointestinal tract occurs. It undergoes extensive first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 35 pg/ml (range 21-52 pg/ml) within 5-8 hours after intake of 1 Kliovance tablet. The half-life of 17 β -oestradiol is about 12-14 hours. It circulates bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound.

Biotransformation and elimination of 17 β -estradiol

Metabolism of 17 β -oestradiol occurs mainly in the liver and the gut but also in target organs, and involves the formation of less active or inactive metabolites, including oestrone, catecholestrogens and several oestrogen sulphates and glucuronides. Oestrogens are excreted with the bile, hydrolysed and reabsorbed (enterohepatic circulation), and mainly eliminated in urine in biologically inactive form.

Absorption and distribution of norethisterone acetate

After oral administration norethisterone acetate is rapidly absorbed and transformed to norethisterone (NET). It undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 3.9 ng/ml (range 1.4-6.8 ng/ml) within 0.5-1.5 hours. The terminal half-life of NET is about 8-11 hours. NET binds to SHBG (36%) and to albumin (61%).

Biotransformation and elimination of norethisterone acetate

The most important metabolites are isomers of 5 α -dihydro-NET and of tetrahydro-NET, which are excreted mainly in the urine as sulfhate or glucuronide conjugates.

The pharmacokinetics of oestradiol is not influenced by norethisterone acetate.

The pharmacokinetic properties in the elderly have not been studied.

5.3 Preclinical safety data

The toxicity profiles of oestradiol 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 datasheet.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize starch

Copolyvidone.

Talc

Magnesium stearate

Hypromellose

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life for Kliovance tablets is 24 months.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate.

Store in a dry place.

Keep the container in the outer carton in order to protect from light.

Keep out of reach of children.

Package Quantities

Kliovance is supplied in a carton of three calendar dial packs containing 28 tablets.

Nature and Contents of Container

The calendar dial pack with 28 tablets consists of the following three parts:

- The base made of coloured non-transparent polypropylene
- The ring-shaped lid made of transparent polystyrene
- The centre-dial made of coloured non-transparent polystyrene

USER INSTRUCTIONS

How to use the calendar pack

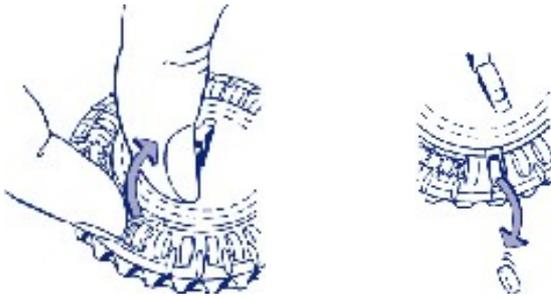
1. Set the day reminder

Turn the inner disc to set the day of the week opposite the little plastic tab.



2. How to take the first day's tablet

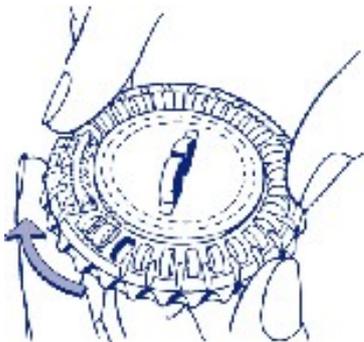
Break the plastic tab and tip out the first tablet.



3. Move the dial every day

On the next day, simply move the transparent dial clockwise 1 space as indicated by the arrow. Tip out the next tablet. Remember to take only 1 tablet once a day.

You can only turn the transparent dial after the tablet in the opening has been removed.



6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

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CCDS v15.0

Kliovance is a trade name owned by Novo Nordisk Health Care AG

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information