SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clinorette

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

17-β oestradiol 2 mg (white tablets)

17-β oestradiol 2 mg and norethisterone 1 mg (pink tablets)

3 PHARMACEUTICAL FORM

Calender pack consisting of 16, round, white, biconvex, film coated tablets and 12 round, pink, biconvex film coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in peri- and post-menopausal women with an intact uterus.

4.2 Posology and method of administration

Clinorette is continuous sequential HRT product. The calendar pack consists of 28 tablets. The 16 white tablets contain 2 mg of 17-β oestradiol and the 12 pink tablets contain 2 mg of 17-β oestradiol and 1 mg of norethisterone. One tablet is taken each day; a treatment cycle consists of 28 days. A menstrual type vaginal bleed usually occurs at the end of the treatment cycle or after administration of the last pink, norethisterone containing, tablet.

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestagen in hysterectomised women.

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.

Starting Clinorette
Menstruating women take the first tablet on the fifth day of menstrual bleeding. If menstruation has stopped, or is infrequent or sporadic, the first tablet can be taken at any time. Patients changing from a cyclic or continuous sequential preparation should complete the cycle and then start *Clinorette* without a break in therapy. Patients changing from a continuous combined

preparation may start therapy at any time if amenorrhoea is established, or otherwise start on the first day of bleeding.

Missed doses
If a dose is forgotten the patient should be advised to take it as soon as they remember. However, if a whole day has passed, patients should be advised not to take the missed tablet but to continue to take one tablet daily. A missed dose may increase the likelihood of break-through bleeding and spotting.

Children or males: Clinorette is not intended for children or males.

Use in the elderly: There are no special dosage requirements.

4.3 Contraindications

Known, past or suspected breast cancer;

Known or suspected oestrogen dependent malignant tumours (e.g. endometrial cancer);

Undiagnosed genital bleeding;

Untreated endometrial hyperplasia;

Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);

Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);

Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;

Known hypersensitivity to the active substances or to any of the excipients;

Porphyria;

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

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 (section 4.3) and warnings (section 4.4) 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 Clinorette, 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. 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 when 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

The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.

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

Breast cancer

A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies including the Million Women Study (MWS) have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years (see Section 4.8). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or oestradiol (E2) was greater when a progestogen was

added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

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

Venous thromboembolism

HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two to threefold higher risk for users compared with non-users. For non-users, it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (Body Mass Index > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the role of varicose veins in VTE.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all post-operative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible. Treatment should not be re-started until the woman is completely mobilised.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxy-progesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore it is uncertain whether these findings also extend to other HRT products.

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA (medroxyprogesterone acetate). 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 1000 women aged 50-59 years and 11 per 1000 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 1000 users aged 50-59 years and between 1 and 9 (best estimate 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer

Long-term (at least 5-10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than oestrogen-only products.

Other conditions

Oestrogens 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 Clinorette is increased.

Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy since rare cases of large increases in 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 radio-immunoassay) or T3 levels (by radioimmunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/ renin substrate, alpha-1-antitrypsin, ceruloplasmin).

There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

Clinorette is not an oral contraceptive neither will it restore fertility. Women of child bearing potential should be advised to adhere to non-hormonal contraceptive methods.

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 (e.g. Phenobarbital, phenytoin, carbamazepine) and antiinfectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (Hypericum perforatum) may induce the metabolism of oestrogens and progestogens.

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

4.6 Pregnancy and lactation

Clinorette is not indicated during pregnancy. If pregnancy occurs during medication with Clinorette, treatment should be withdrawn immediately. Data on a limited number of exposed pregnancies indicate adverse effects of norethisterone on the foetus. At doses higher than normally used in OC and HRT formulations, masculinisation of female foetuses has been observed.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens with progestogens, indicate no teratogenic or foetotoxic effects.

Clinorette is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines are reported.

4.8 Undesirable effects

Genito-urinary system – breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhoea, premenstrual like syndrome, increase in size of uterine

fibroids, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis like syndrome.

Breasts – tenderness, enlargement, secretion, breast cancer (see below)

Gastrointestinal – nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice.

Skin – chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, haemorrhagic eruption, loss of scalp hair, hirsutism.

Eyes – steepening of corneal curvature, intolerance to contact lenses.

CNS – headaches, migraine, dizziness, mental depression, chorea.

Miscellaneous – increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, oedema, change in libido, leg cramps.

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.

- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.

- The level of risk is dependent on the duration of use (see section 4.4).

- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

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

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

#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

*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 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users over 5 years (95% CI)
CEE Oestrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
CEE + MPA Combined oestrogen & progestagen#			
50-79	17	1.2 (1.0 – 1.5)	+4 (0-9)

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

*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 1000 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 epidemiology studies varied from

between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

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

Ovarian cancer

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

Risk of venous thromboembolism

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

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

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users
Oral oestrogen-only*			
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 as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

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

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

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

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

4.9 Overdose

Nausea and vomiting may occur after overdosage. Treatment should be symptomatic; there is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 menopausal women, and alleviates menopausal symptoms.

Norethisterone: As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen reduces but does not eliminate the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

5.2 Pharmacokinetic properties

17- β oestradiol is absorbed rapidly after oral administration. The rate and completeness of absorption of 17- β oestradiol from the white oestrogen only tablets contained in Clinorette were found to be bioequivalent to a standard 17- β oestradiol 2mg preparation as assessed by the maximum concentrations

achieved (Clinorette Oestrogen only tablets C_{max} = 187 pmol/L), time to maximum concentration (T_{max}) and area under the concentration time curve (AUC).

The oestrogens and their esters are handled in the body in much the same way as are the endogenous hormones. Inactivation of oestrogen is carried out mainly in the liver. A certain proportion of the oestrogen is excreted into the bile and then reabsorbed from the intestine.

After oral administration, norethisterone is absorbed from the GI tract with peak plasma concentrations occurring at 1 to 2 hours. It undergoes first-pass metabolism by the liver. Norethisterone is highly protein bound (about 60% to albumin and 35% to sex hormone binding globulin (SHBG)). Administration with an oestrogen (as in Clinorette) increases the proportion bound to SHBG.

5.3 Preclinical safety data

Studies in animals have indicated that administration of very high doses of oestrogens will induce neoplastic tumours in some animal species.

The results of preclinical studies of 17- β oestradiol have not suggested any unwanted effects at therapeutic doses used in humans.

Norethisterone, like other progestagens has been shown to cause virilisation of female foetuses in rats and monkeys and embryolethal effects at high doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

17 beta oestradiol tablets:

Lactose EP

Crospovidone USNF

Povidone EP

Talc EP

Magnesium stearate EP

Opadry white Y-1-7000 HSE (methocel E5, titanium dioxide, propylene glycol)

Combination tablet:

Lactose EP

Crospovidone USNF

Povidone EP

Talc EP

Magnesium stearate EP

Opadry white Y-1-7000 HSE (methocel E5, titanium dioxide, propylene glycol)

Erythrosine lake HSE

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25^{o}C in a dry dark place

6.5 Nature and contents of container

PVC and aluminium foil calender blister pack enclosed in a cardboard carton. Each pack contains 28 tablets. A sample pack of 28 tablets.

6.6 Special precautions for disposal

None stated

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PL 21812/0002

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