SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cliovelle 1 mg/0.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains estradiol 1 mg (as estradiol valerate) and norethisterone acetate 0.5 mg.
Excipient with known effect: lactose 65.78 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, round, biconvex tablets, 6 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone Replacement Therapy (HRT) for estrogen deficiency symptoms in women more than one year after menopause.

Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis (see also section 4.4).

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

4.2 Posology and method of administration

Posology
Cliovelle is a preparation for the continuous combined hormone replacement treatment of women with an intact uterus. One tablet is taken daily without interruption, preferably at the same time of 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.

Changing over to a combination product with a higher dose should be considered if after 3 months the treatment has not resulted in satisfactory symptom relief.

Method of administration
Oral use.

Women with amenorrhoea not taking HRT or women transferring from another continuous combined HRT product can start treatment with Cliovelle on any convenient day. For women transferring from sequential preparations the treatment should be started immediately after withdrawal bleeding has stopped.

Missed dose
If the patient forgets to take a tablet she can take it within 12 hours of the usual time, otherwise the forgotten tablet must be discarded. Missed doses can increase the likelihood of breakthrough bleeding and spotting.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- 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.

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 reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see ‘Breast cancer’ below). Investigations, including 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 Cliovelle, in particular:
- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumours, e.g. first degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus (SLE)
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy
Therapy should be discontinued in case a contraindication (see section 4.3) is discovered and in the following situations:
- Jaundice (icterus) or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

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

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

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
The overall evidence shows an increased risk of breast cancer in women taking combined estrogen-progestagen or estrogen-only HRT, that is dependent on the duration of taking HRT.

Combined estrogen-progestagen therapy
The randomised placebo-controlled trial the "Women's Health Initiative Study" (WHI) and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progestagen for HRT that becomes apparent after about 3 (1-4) years (see section 4.8).

Estrogen-only therapy
The WHI trial found no increase in the risk of breast cancer in hysterectomised women using estrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is lower than that found in users of estrogen-progestagen combinations (see section 4.8).

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

HRT, especially estrogen-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 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 the use of combined HRT may be associated with a similar or slightly smaller risk (see section 4.8).

Venous thromboembolism
HRT is associated with a 1.3 - 3-fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (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 estrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.
As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery 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 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 contraincidicated (see section 4.3).

Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

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

Coronary artery disease (CAD)
There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestagen or estrogen-only HRT.

Combined estrogen-progestagen therapy
The relative risk of CAD during use of combined estrogen+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 estrogen+progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Estrogen-only therapy
Randomised controlled data found no increased risk of CAD in hysterectomised women using estrogen-only therapy.

Ischaemic stroke
Combined estrogen-progestagen and estrogen-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
Estrogens 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 estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Estrogens 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 radioimmunoassay, RIA) or T3 levels (by RIA). 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).

Patients who require thyroid hormone replacement therapy should have their thyroid function monitored regularly while on HRT to ensure that thyroid hormone levels remain in an acceptable range.

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 estrogen-only HRT after the age of 65.

Hepatitis C
During clinical trials with the hepatitis C virus (HCV) combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.
Women using medicinal products containing estrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

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 anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and antiinfectives (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 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 metabolizing enzymes, e.g. ketoconazole, may increase circulating levels of the active substances of Cliovelle.

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

Effect of HRT with estrogens on other medicinal products
Hormone contraceptives containing estrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

Pharmacodynamic interactions
Direct acting antiviral agents (DAAs) and ethinylestradiol-containing medicinal products such as CHCs
During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.

Direct acting antiviral agents (DAAs) and medicinal products containing estrogens other than ethinylestradiol, such as estradiol
Women using medicinal products containing estrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of women taking these other estrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Cliovelle is not indicated during pregnancy. If pregnancy occurs during medication with Cliovelle, treatment should be withdrawn immediately.

Data on a limited number of exposed pregnancies indicate no adverse effects of norethisterone acetate on the fetus. At higher doses than normally used in contraceptives 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.

Breastfeeding
Cliovelle is not indicated during breastfeeding.

Fertility
No data are available.

4.7 Effects on ability to drive and use machines

Cliovelle has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most common undesirable effects reported in clinical trials with estradiol valerate and norethisterone acetate were vaginal bleeding and breast pain/tenderness, reported in approx. 10-20 % of patients. Vaginal bleeding usually occurred during the first months of treatment. Breast pain

usually disappeared after a few months. All the undesirable effects observed in randomised clinical studies at a greater frequency for estradiol valerate and norethisterone acetate than for placebo and assessed as possibly being associated with the treatment are set out in the table below.

The observed adverse reactions are ranked in order of decreasing frequency within the system organ class.

Within each frequency grouping, adverse drug reactions are presented in the order of decreasing seriousness.

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**
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"		Anaphylactic reaction
Metabolism and nutrition disorders		Fluid retention, see also "General disorders and administration site conditions"			
Psychiatric disorders		Depression or depression aggravated	Nervousness		
Nervous system disorders		Migraine or migraine aggravated headache			
Vascular disorders			Superficial thrombophlebitis	Pulmonary embolism, venous thromboembolism	
Gastrointestinal disorders		Nausea	Abdominal pain, abdominal distension or abdominal discomfort, flatulence or bloating		
Skin and subcutaneous tissue disorders			Hirsutism or acne, alopecia, urticaria or pruritus		
Musculoskeletal and connective tissue disorders		Back pain	Leg cramps		
Reproductive system and breast disorders	Vaginal haemorrhage, breast pain or breast tenderness	Breast oedema or breast enlargement; uterine fibroids or enlarged or recurrent uterine fibroids			
General disorders and administration site conditions		Peripheral oedema			
Investigations		Weight increased			

<u>Breast cancer risk</u>
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.

The increased risk in users of estrogen-only therapy is lower than that seen in users of estrogen-progestagen combinations.

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

Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI study) and the largest meta-analysis of prospective epidemiological studies are presented.

Largest meta-analysis of prospective epidemiological studies
Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)*	Risk ratio	Additional cases per 1000 HRT users after 5 years
Estrogen only HRT			
50	13.3	1.2	2.7
Combined estrogen-progestagen			
50	13.3	1.6	8.0

* *Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)*
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years)*	Risk ratio	Additional cases per 1000 HRT users after 10 years
Estrogen only HRT			
50	26.6	1.3	7.1
Combined estrogen-progestagen			
50	26.6	1.8	20.8

* *Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)*
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 & 95 % CI	Additional cases per 1000 HRT users over 5 years (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.*

Endometrial cancer
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 estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).
Depending on the duration of estrogen-only use and estrogen 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 estrogen-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
Use of estrogen-only or combined estrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

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

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

US 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 & 95 % CI	Additional cases per 1000 HRT users over 5 years
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 section 4.4).

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. The risk of haemorrhagic stroke is not increased during use of HRT.

This relative risk is dependent on age and 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.

US 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 & 95 % CI	Additional cases per 1000 HRT users over 5 years
50 - 59	8	1.3 (1.1 - 1.6)	3 (1 - 5)

* *No differentiation was made between ischaemic and haemorrhagic stroke.*

Other adverse reactions have been reported in association with estrogen/progestagen treatment:
- Gall bladder disease;
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum and vascular purpura;
- Probable dementia over the age of 65 (see section 4.4);
- Dry eyes;
- Tear film composition changes.

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

4.9 Overdose

Symptoms of overdosage with oral estrogens are breast tenderness, nausea, vomiting and/or metrorrhagia. Overdosage of progestagens may lead to a depressive mood, fatigue, acne and hirsutism. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestagens and estrogens, fixed combinations, ATC code: G03FA01

Estrogen and progestagen for continuous combined replacement treatment (HRT).

Estradiol: The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of estrogen production in menopausal women and alleviates menopausal symptoms.

Estrogens prevent bone loss following menopause or ovariectomy.

Norethisterone acetate: As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical trial information

Cliovelle is bioequivalent to 1 mg estradiol/0.5 mg norethisterone acetate containing reference tablets for which clinical trial data are available.

- Relief of estrogen-deficiency symptoms and bleeding patterns

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

Cliovelle is a preparation for combined continuous HRT administered with the intention of avoiding the regular withdrawal bleeding that occurs in cyclical or sequential HRT. Amenorrhea was seen in 90 % of the women during months 9-12 of treatment. Irregular bleeding and/or spotting appeared in 27 % of the women during the first three months of treatment and in 10 % during months 10-12 of treatment.

- Prevention of osteoporosis

Estrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of estrogens 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.

After 2 years of treatment with 1 mg estradiol/0.5 mg norethisterone acetate, the mean increase in lumbarspine bone mineral density (BMD) from baseline was 3.8 % (95 % confidence interval 2.8 % to 4.9 %) in one published trial and 6.4 % (3.8 % to 6.9 %) in another published trial. The percentage of women who maintained or gained BMD in lumbar zone during treatment was 87 % in one trial.

Tablets with 1 mg estradiol/0.5 mg norethisterone acetate also had an effect on hip BMD. The increase from baseline at femoral neck after 2 years was 1.8 % ± 4.1 % (mean ± SD), $p < 0.05$ compared to baseline) in one trial, but only 0.7 % (95 % confidence interval -1.3 % to 2.8 %, $p < 0.18$ compared to placebo) in another where, however, a mean BMD increase at total hip after 2 years of 3.3 % (1.7 % to 5.0 %, $p < 0.001$ compared to placebo) was shown.

5.2 Pharmacokinetic properties

Estradiol valerate
Since estradiol valerate is rapidly cleaved in the small intestine, the intestinal mucosa and the liver, its pharmacokinetic properties correspond to those of orally administered estradiol.

Estradiol is rapidly and completely absorbed from the gastrointestinal tract after oral administration. The maximum plasma concentration is generally achieved 5 - 8 hours after ingestion. The plasma elimination half-life is about 12 - 14 hours. Estradiol circulates in the blood bound to SHBG (37 %) and albumin (61 %), with only 1 - 2 % not being bound. The metabolism of estradiol predominantly takes place in the liver and in the intestine, but also in the target organs. Estradiol is mainly converted to estrone and estriol. These are excreted into the bile and undergo enterohepatic recirculation and further degradation before being excreted in the urine (90 - 95 %) as biologically inactive glucuronide and sulfate conjugates or mostly unconjugated in the faeces (5 - 10 %).

Norethisterone acetate
Norethisterone acetate (NETA) is absorbed from the gastrointestinal tract and its effects last at least 24 hours. The maximum blood concentration is generally achieved 1 - 4 hours after oral administration. Norethisterone acetate undergoes a first-pass effect, being transformed to norethisterone, which is then metabolized and eliminated, predominantly in the urine, as glucuronide and sulfate conjugates. Approximately 97 % of unmetabolized norethisterone in the serum is protein-bound. Of this 61 % is bound to albumin and 36 % to SHBG. The half-life of unmetabolized norethisterone in the plasma is on average 10.15 hours (SD ± 5.46).

Bioequivalence was demonstrated in a study performed with Cliovelle and 1 mg estradiol/0.5 mg norethisterone acetate containing reference tablets.
After taking a single dose Cliovelle the arithmetical mean value of C_{max} was 5.23 (SD ± 2.26) ng/ml for norethisterone and 21.6 (SD ± 8.9) pg/ml for estradiol.

5.3 Preclinical safety data

The acute toxicity of estrogens is low. Due to the great differences between animal species and between animals and humans preclinical results are of limited value for predicting the effect on humans.

Animal studies have shown embryo-lethal effects of estradiol or estradiol valerate even at relatively low doses; malformations of the urogenital tract and feminization of male fetuses were observed.

Like other progestagens norethisterone causes virilization of female fetuses in rats and monkeys. At high doses of norethisterone embryo-lethal effects were observed.

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. Long-term, continuous administration of norethisterone in certain animal species increases the frequency of tumours of the hypophysis and ovary in females, and of liver and breast in males.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copovidone
Lactose monohydrate
Magnesium stearate
Maize starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blister packs.
Calendar blister packs of 28 and 84 tablets.
Blister packs of 30 and 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 February 2006
Date of latest renewal: 3 February 2011

10. DATE OF REVISION OF THE TEXT

2025-06-24