SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Elleste Duet Conti Tablets
2 mg/1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2 mg estradiol (as estradiol hemihydrate) and 1 mg norethisterone acetate.
Excipient with known effect: 60.8 mg lactose monohydrate.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Grey, round, biconvex tablets embossed with ‘P2’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in women one year since last menses. 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
For initiation and continuation of treatment of post-menopausal symptoms the lowest
effective dose for the shortest duration (see also Section 4.4) should be used.

The product is a continuous combined HRT. One grey tablet is taken daily.
The oestrogen and the progestogen are given every day without interruption.

Therapy may start at any time in patients without prior hormone replacement therapy. Patients changing from another cyclical or continuous sequential preparation should complete the cycle and may then change to Elleste Duet Conti Tablets 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 Tablet: If a tablet is missed it should be taken within 12 hours of when normally taken; otherwise the tablet should be discarded, and the usual tablet should be taken the following day. If a tablet is missed there is an increased likelihood of breakthrough bleeding or spotting.

Elderly

There are no special dosage requirements in elderly patients

Paediatric population

Not to be used in children.

Method of administration
For oral use.

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 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 Sections 4.3 Contraindications and 4.4 Special warnings and precautions 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 Elleste Duet Conti Tablets, 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 (eg, 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 and Carcinoma

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, risk may remain elevated for at least 10 years.

The addition of a progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-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 oestrogen-progestogen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestogen 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 oestrogen-progestogen for HRT that becomes apparent after about 3 (1 – 4) years (see Section 4.8).

Oestrogen-only therapy

- The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-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 oestrogen-progestogen 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 oestrogen-progestogen 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 the 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 1.3-3 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>30kg/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 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)

- There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT.

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

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

Ischaemic Stroke

- Combined oestrogen-progestogen 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).

Hypothyroidism

- 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.

Angioedema

- Oestrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

Other Conditions

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

- Women with pre-existing hypertriglyceridemia 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 oral oestrogen therapy in this condition.

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

- 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, ceruloplasmin).

- HRT 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.

ALT elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and 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 oestrogens 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 oestrogens; however, due to the limited number of women taking these other oestrogens, 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.

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 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 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 progestogens.

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

Some laboratory tests can be influenced by oestrogens, such as tests for thyroid function (see Section 4.4).

Effect of HRT with oestrogens on other medicinal products
Hormone contraceptives containing oestrogens 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
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 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 oestrogens 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 oestrogens; however, due to the limited number of women taking these other oestrogens, 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).

4.6 Fertility, pregnancy and lactation

Pregnancy:

Elleste Duet Conti Tablets are not indicated during pregnancy. If pregnancy occurs during medication with Elleste Duet Conti Tablets, treatment should be withdrawn immediately.
Clinically, data on a limited number of exposed pregnancies indicate no adverse effects of norethisterone acetate on the foetus. At doses higher than 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 progestogens indicate no teratogenic or foetotoxic effect.

Breast-feeding:

Elleste Duet Conti Tablets are not indicated during breast-feeding.

4.7 Effects on ability to drive and use machines

Elleste Duet Conti Tablets have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse experiences are breast tension and pain, dysmenorrhoea, irregular bleeding, and headache.

Within each frequency grouping, adverse drug reactions are presented in the order of decreasing seriousness. 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); not known (cannot be estimated from the available data).

System organ class (MedDRA SOC level)	***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)***	***not known** (cannot be estimated from the available data)***
Immune system disorders				Hyper-sensitivity		
Psychiatric disorders		Depression*, nervousness*, affect lability, libido disorder				
Nervous system disorders	Headache*	Dizziness*, insomnia*	Migraine, vertigo	Paraesthesia		
Vascular disorders			Hypertension, varicose veins	Embolism venous***, thrombo-phlebitis		
Gastrointestinal disorders		Nausea, abdominal distension*, diarrhoea*, dyspepsia*, abdominal pain	Vomiting			
Hepatobiliary disorders			Gallbladder disorder, cholelithiasis		Jaundice cholestatic	
Skin and subcutaneous tissue disorders		Acne*, rash, pruritus*, dry skin	Skin discoloration		Hirsutism	Alopecia
Musculoskeletal and connective tissue disorders		Back pain*, pain in extremity*	Muscle spasms	Myasthenia		
Reproductive system and breast disorders	Breast pain*, breast tenderness, dysmenorrhoea*, menstrual disorder*	Breast enlargement*, menorrhagia*, genital discharge *, irregular	Breast cancer	Uterine leiomyoma, fallopian tube cysts, endocervical polyps		

		vaginal bleeding, uterine spasms, vaginal infection, endometrial hyperplasia				
General disorders and administration site conditions		Pain, asthenia, oedema peripheral*, weight increased*				
Investigations			Transaminases increased			

(*) Adverse reactions associated with oestrogen and progestogen have been found to be relatively less frequent with the lowest dosage strength.
(**) Reported in post-marketing experience.
(***)Venous thromboembolism i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see section 4.3 Contraindications and 4.4 Special warnings and precautions for use.

Breast Cancer Risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.
- The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestogen 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
		Oestrogen only HRT	
50	13.3	1.2	2.7
		Combined oestrogen-progestogen	
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
		Oestrogen only HRT	
50	26.6	1.3	7.1
		Combined oestrogen-progestogen	
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 (yrs)	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 oestrogen-only	
50-79	21	0.8(0.7-1.0)	-4(-6-0)*
		CEE+MPA oestrogen & progestogen‡	
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

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 progestogen 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

Use of oestrogen-only or combined oestrogen-progestogen 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 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 over 5 years
Oral oestrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined oestrogen-progestogen			
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-progestogen HRT over the age of 60 (see Section 4.4).

Risk of Ischaemic Stroke

- The use of oestrogen-only and oestrogen - progestogen 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 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 oestrogen-progestogen treatment:

- skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of over dosage with oral oestrogens are breast tenderness, nausea, vomiting and/or metrorrhagia. Over dosage of progestogens may lead to a depressive mood, fatigue, acne and hirsutism. If over dosage is discovered within two or three hours and is so large that treatment seems desirable, gastric lavage can be considered. There are no specific antidotes for over dosage and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and oestrogens, combinations
ATC code: G03F A01.

Estradiol

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

Oestrogens prevent bone loss following menopause or ovariectomy. 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 progestogen – 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.

Norethisterone acetate

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non hysterectomised women.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters for Elleste Duet Conti Tablets (2 mg estradiol + 1 mg norethisterone tablets) are provided in the table below. The data were obtained from an open label, two way crossover pharmacokinetic study in which treatment was administered for 7 days to achieve steady state (n=24). Pharmacokinetic data were collected over 24 hours.

	Serum unconjugated estradiol mean (SD)	**Serum unconjugated estrone mean (SD)**	**Norethisterone mean (SD)**
AUC_{0-24h}	967.8 (0.5) pg.h/ml	8366 (1.7) pg.h/ml	43.2 (0.4) ng.h/ml
C_{max}	61.6 (0.4) pg/ml	648.5 (1.5) pg/ml	11.8 (0.4) ng/ml

C_{min}	19.3 (0.6) pg/ml	131.1 (2.5) pg/ml	0.5 (0.5) ng/ml
T_{max}	3.4 (2.1) h	5.07 (1.8) h	0.9 (0.3) h

Estradiol
Readily and fully absorbed from the GI tract when given orally, peak levels are generally observed 3-6 hours after ingestion, but by 24 hours concentrations have returned to baseline.
Estradiol is converted to estrone and estriol primarily in the liver. 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 sulphate conjugates or in the faeces (5-10%), mostly unconjugated.

Norethisterone acetate
Norethisterone acetate is absorbed from the GI tract and its effects last for at least 24 hours. Maximum blood concentrations are generally reached 1-4 hours after administration. Norethisterone acetate undergoes first pass effect, being transformed to norethisterone which is then metabolised and excreted mainly in the urine as glucuronide and sulphate conjugates.

5.3 Preclinical safety data

Both estradiol and norethisterone acetate have been shown to induce adverse effects in preclinical reproductive toxicity studies. Chiefly, estradiol showed embryotoxic effects and induced anomalies in urogenital tract development, e.g. feminisation of male foetuses in high doses. Norethisterone acetate showed embryotoxic effects and induced anomalies in urogenital tract development. In mice, additional anomalies in non-urogenital foetal development, including hydrocephalus and clubfoot, have been detected.

Long-term, continuous administration of natural and synthetic oestrogens 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

Tablet core:

Lactose monohydrate
Maize starch
Povidone 25

Talc (purified)
Magnesium stearate.

Film-coating material:

Hydroxypropylmethyl cellulose (E464)
Titanium dioxide (E171)
Macrogol 400
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Aluminium foil and PVC blister packed in a cardboard carton.
Pack sizes: 28 film-coated tablets and 84 (3 x 28) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Exeltis Healthcare S.L.
Avda. de Miralcampo 7
Pol. Ind. Miralcampo, 19200-Azuqueca de Henares (Guadalajara)
Spain

8 MARKETING AUTHORISATION NUMBER(S)

PL 44081/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 November 1997
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10 DATE OF REVISION OF THE TEXT

13/06/2025