SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Elleste Solo 1 mg Tablets
1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg estradiol (as estradiol hemihydrate)

Excipient with known effect: 62.8 mg lactose monohydrate

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, round biconvex tablets, marked with ‘01’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in post- and peri-menopausal women (see also Section 4.4).
The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Posology

One tablet daily to be taken orally. Elleste Solo 1 mg may be taken continuously in hysterectomised women. In women with a uterus, a progestogen should be added for 12 - 14 days each cycle to oppose the production of an oestrogen-stimulated hyperplasia of the endometrium. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

Therapy may start at any time in women with established amenorrhoea or who are experiencing long intervals between spontaneous menses. In patients who are menstruating, it is advised that therapy starts on the first day of bleeding. Patients changing from a cyclical or continuous sequential preparation should complete the cycle and may then change to Elleste Solo 1 mg 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.

Elleste Solo tablets are available in two strengths: Elleste Solo 1 mg (containing 1 mg estradiol) and Elleste Solo 2 mg (containing 2 mg estradiol). For initiation and continuation of treatment of post-and peri-menopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used. Elleste Solo 2 mg is additionally indicated for prevention of osteoporosis in postmenopausal women at high risk of future fractures and who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

Missed or Extra 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. A missed dose may lead to break-through bleeding or spotting in non-hysterectomised women. If one extra tablet is taken inadvertently, the usual tablet should be taken the following day.

Elderly

There are no special dosage requirements for 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 idiopathic 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;
Known 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 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 Solo 1 mg, 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 if 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.

For oral doses of estradiol >2 mg and patches >50 µg/day the endometrial safety of added progestogens has not been demonstrated.

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.
Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

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-progestogen 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>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 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).

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

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 Solo 1 mg is not indicated during pregnancy. If pregnancy occurs during medication with Elleste Solo 1 mg treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to

inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

Lactation:

Elleste Solo 1 mg is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Elleste Solo 1mg Tablets have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects observed with oestrogens are detailed in the following table. The effects are grouped according to system organ class.

Organ System Class	Common ADRs, >1/100,<1/10	Uncommon ADRs >1/1,000, <1/100	Rare ADRs >1/10,000, <1/1,000	Frequency unknown*
Infections and infestations		Vaginal candidiasis		
Immune system disorders		Hypersensitivity		
Metabolism and nutrition disorders	Weight increased, weight decreased			
Psychiatric disorders	Mood alterations including anxiety and depressed mood, libido disorder			
Reproductive	Metrorrhagia,	Breast pain	Dysmenorrhoea,	Fibrocystic breast

system and breast disorders	breast tenderness, breast enlargement, Uterine/vaginal bleeding including spotting		vaginal discharge, premenstrual syndrome	disease
Gastrointestinal disorders	Nausea, abdominal pain	Dyspepsia, vomiting, flatulence		Pancreatitis (in women with pre-existing hypertriglyceridaemia) Gastroesophageal reflux disease
Hepatobiliary disorders		Gallbladder disorder, cholelithiasis		Hepatic function abnormal, sometimes with jaundice
Nervous System disorders	Headache	Dizziness, migraine		Probable dementia over the age of 65 (see section 4.4), chorea, exacerbation of epilepsy
Eye disorders		Visual disturbances	Contact lens intolerance	
Cardiac disorders		Palpitations		
Skin and subcutaneous tissue disorders	Rash, pruritus	Erythema nodosum, urticaria	hirsutism, acne	Angioedema, Erythema multiforme, Vascular purpura, Chloasma
Musculoskeletal and connective tissue disorders			Muscle cramps	
General disorders and administration site conditions	Oedema			
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)				Breast cancer[a] Oestrogen dependent neoplasms benign and malignant, e.g. endometrial cancer[b], ovarian cancer[c] Increase in size of leiomyoma
Vascular disorders				Stroke [f] Arterial thromboembolism, i.e. angina and myocardial

				infarction[e]. For further information see sections 4.3 and 4.4. Venous thromboembolism[d], i.e. deep leg or pelvic venous thrombosis and pulmonary embolism. For further information see sections 4.3 and 4.4.
Renal and urinary disorders				Urinary incontinence

*Undesirable effects from spontaneous post-marketing reporting sources, which have not been observed in clinical trials.

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 perspective 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)

‡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 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

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

Nausea, vomiting, sleepiness, dizziness and withdrawal bleeding may occur in some women. There is no specific antidote and treatment should be symptomatic.
Aforementioned information is also applicable for overdosing in children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural and semisynthetic oestrogens, plain
ATC Code: G03CA03.

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.

5.2 Pharmacokinetic properties

No pharmacokinetic parameters are available for Elleste Solo 1 mg. Pharmacokinetic parameters for Elleste Solo 2 mg, are provided in the following table. Elleste Solo 2 mg contains 2 mg estradiol (as hemihydrate). The data were obtained from an open label, single dose, two way crossover pharmacokinetic study (n=16). Pharmacokinetic data were collected over 48 hours.

	Plasma Unconjugated Estradiol (mean)	**Plasma Unconjugated Estrone (mean)**
$AUC_{0\text{-}48h}$	950 pg.h/ml	2700 pg.h/ml
C_{max}	45 pg/ml	140 pg/ml
T_{max}	5.0 h	4.0 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.

5.3 Preclinical safety data

Estradiol has 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.

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

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: 20, 28, 60, 84 or 100 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 44081/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/08/2007

10 DATE OF REVISION OF THE TEXT

13/06/2025