SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ethinylestradiol Tablets BP 10 mcg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ethinylestradiol 10.5 micrograms

Excipients with known effect: Lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White, biconvex, uncoated tablets, engraved “EVANS 136” on one side, plain on the reverse.

4.1 Therapeutic indications

Ethinylestradiol Tablets are indicated in adults for:

- post menopausal symptoms due to estrogen deficiency.
- 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.
- palliative treatment of prostatic cancer.
- hormone replacement therapy for failure of ovarian development e.g. in patients with gonadal dysgenesis where initial estrogen therapy is later followed by combined estrogen/progestogen therapy.
- disorders of menstruation, given in conjunction with a progestogen.

(See also Section 4.4).

4.2 Posology and method of administration

Posology

Ethinylestradiol Tablets is an estrogen-only preparation of hormone replacement therapy (HRT) for oral administration.

Post menopausal symptoms due to estrogen deficiency including prevention of postmenopausal osteoporosis: 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. The usual dose range is 10 to 50 micrograms daily, usually on a cyclical basis (e.g., 3 weeks on and 1 week off).

For women without a uterus, who did not have endometriosis diagnosed, it is not recommended to add a progestogen.

In women with an intact uterus (or in endometriosis when endometrial foci may be present despite hysterectomy), where a progestogen is necessary, it should be added for at least 12-14 days every month/28 day cycle to reduce the risk to the endometrium.

The benefits of the lower risk of endometrial hyperplasia and endometrial cancer due to adding progestogen should be weighed against the increased risk of breast cancer (see Sections 4.4 and 4.8).

Therapy with Ethinylestradiol Tablets may start at any time in women with established amenorrhoea or who are experiencing long intervals between spontaneous menses. In women who are menstruating, it is advised that therapy starts on the first day of bleeding. As Ethinylestradiol Tablets are usually taken on a cyclical basis direct switching from other estrogen-only HRT preparations taken cyclically is possible.

Palliative treatment of prostatic cancer: 150 micrograms to 1.5 mg daily. Larger dose Ethinylestradiol Tablets are available.

Hormone replacement therapy for failure of ovarian development e.g. in patients with gonadal dysgenesis: 10 to 50 micrograms daily, usually on a cyclical basis. Initial estrogen therapy should be followed by combined estrogen/progestogen therapy.

Disorders of menstruation: 20 to 50 micrograms daily from day 5 to day 25 of each cycle. A progestogen is given daily in addition, either throughout the cycle or from days 15 to 25 of the cycle.

If a dose is forgotten it should be taken as soon as it is remembered. If it is nearly time for the next dose then the patient should wait until then. Two doses should not be taken together. Forgetting a dose may increase the likelihood of break-through bleeding and spotting.

Elderly

As for adults.

Paediatric population

There is no relevant use for Ethinylestradiol in the paediatric population.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Active or recent arterial thromboembolic disease, e.g. angina, myocardial infarction
- Current or previous idiopathic venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known, past or suspected breast cancer or other known or suspected estrogen dependent tumours (e.g. endometrial cancer)
- Untreated endometrial hyperplasia
- Undiagnosed genital bleeding
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Porphyria
- Known hypersensitivity to the active substance or to any of the excipients
- Concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.4 and section 4.5).

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 benefit outweighs the risk.

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications 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). Investigation, 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 ethinylestradiol tablets, in particular:

- Risk factors for estrogen dependent tumours e.g. 1st degree heredity for breast cancer
- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below)
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes Mellitus with or without vascular involvement

- Cholelithiasis
- Otosclerosis
- Asthma
- Migraine or (severe) headache and epilepsy
- Systemic Lupus erythematosis
- Hyperplasia of the endometrium (see below)

Reasons for immediate withdrawal of therapy

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Endometrial hyperplasia

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

The reduction in risk to the endometrium should be weighed against the increase in the risk of breast cancer of added progestogen (see 'Breast cancer' below and in Section 4.8)

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 estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to estrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis (but see above).

Breast cancer

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

Combined oestrogen-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 oestrogen-progestagen 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-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.

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

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

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

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

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

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

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined continuous estrogens and medroxyprogesterone acetate (MPA). For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50 – 59 years and 11 per 1000 women aged 60 – 69 years. It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50 – 59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60 – 69 years. It is unknown whether the increased risk also extends to other HRT products.

Coronary Artery Disease (CAD)

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

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). ALT elevations have also been observed with HCV anti-viral medicinal products containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.3 and 4.5).

Other conditions

- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Ethinylestradiol Tablets is increased.
- Women with pre-existing hypertriglyceridemia 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.
- 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 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-I-antitrypsin, ceruloplasmin).
- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

- Patients with rare hereditary problems of galactose intolerance, the Lapp-lactose deficiency, or glucose-galactose malabsorption should not take this medicine.
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of estrogens may be increased by concomitant use of substances known to induce drug metabolising enzymes, specifically cytochrome P450 enzymes, such as anti-convulsants (e.g. phenobarbitol, phenytoin, carbamazepine), anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and modafinil.

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St Johns Wort (Hypericum Perforatum) may induce the metabolism of estrogens.

Concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir with or without ribavirin, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir, may increase the risk of ALT elevations (see sections 4.3 and 4.4). Ethinylestradiol can be restarted 2 weeks following completion of treatment with these drug regimens.

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

Ethinylestradiol doses greater than 50 micrograms per day may cause imipramine toxicity in patients on concomitant therapy.

Through its effects on the coagulation system, ethinylestradiol may reduce the effects of anticoagulants such as warfarin, phenindione or nicoumalone.

The doses of insulin or hypoglycaemic drugs may need to be adjusted due to the mild diabetogenic effect of ethinylestradiol.

Ethinylestradiol may inhibit the metabolism of theophylline and reduce its clearance.

Ethinylestradiol has been shown to decrease serum concentrations of lamotrigine when the two drugs are co-administered.

Interaction studies have only been performed in adults.

4.3 Fertility, pregnancy and lactation

Pregnancy

Ethinylestradiol Tablets are not indicated during pregnancy. If pregnancy occurs during medication with Ethinylestradiol Tablets treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent fetal exposure to estrogens indicate no teratogenic or fetotoxic effects.

Breast-feeding

Ethinylestradiol Tablets are not indicated during lactation.

Fertility

Not relevant.

4.4 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Breast cancer risk

- The level of risk is dependent on the duration of use (see Section 4.4)
- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestagen combinations.
- 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-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/m2)

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-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 (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 & 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

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens. According to the data from epidemiological studies, the best estimate of the risk of endometrial cancer is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and estrogen dose, the reported increase in endometrial cancer risk among unopposed estrogen users varies from 2-to 12-fold greater compared with non- users. Adding a progestogen to estrogen-only therapy greatly reduces this this increased risk.

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.

Other adverse reactions have been reported in association with estrogen treatment;

Genito-urinary tract: endometrial neoplasia, endometrial cancer, intermenstrual bleeding, increase in the size of uterine fibromyomata, endometrial proliferation or aggravation of endometriosis, excessive production of cervical mucus.

Breast: tenderness, pain, enlargement, secretion.

Gastro-intestinal tract: nausea, vomiting, cholelithiasis, cholestatic jaundice.

Cardiovascular system: hypertension, thrombosis, thrombophlebitis, thromboembolism, myocardial infarction, stroke.

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.

Skin and Subcutaneous Tissue Disorders: erythema nodosum, erythema multiforme, vascular purpura, rash, chloasma. Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Eyes: corneal discomfort if contact lenses are used.

CNS: headache, migraine, mood changes (elation or depression), probable dementia (see Section 4.4).

Metabolic: sodium and water retention, reduced glucose tolerance and change in body weight, hypercalcaemia.

In men: feminisation, gynaecomastia, testicular atrophy and impotence.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.5 Overdose

Symptoms

Acute overdose of ethinylestradiol may cause nausea and vomiting and may result in withdrawal bleeding in females.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Estrogens , ATC code: G03CA01

Mechanism of action

The active ingredient, ethinylestradiol, is chemically and biologically identical to endogenous human oestradiol. It substitutes for the loss of estrogen production in

menopausal women, and alleviates menopausal symptoms. Estrogens prevent bone loss following menopause or ovariectomy.

Clinical efficacy and safety

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 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.

The main therapeutic use of exogenous estrogens is replacement in deficiency states.

5.2 Pharmacokinetic properties

Absorption

Ethinylestradiol is rapidly and completely absorbed from the gut but it undergoes some first pass metabolism in the gut wall.

Distribution

Ethinylestradiol is rapidly distributed throughout most body tissues with the largest concentration found in adipose tissue. It distributes into breast milk in low concentrations. More than 80% of ethinylestradiol in serum is conjugated as the sulphate and almost all the conjugated form is bound to albumin.

Elimination

Ethinylestradiol is metabolised in the liver. Hydroxylation appears to be the main metabolic pathway. 60% of a dose is excreted in the urine and 40% in the faeces. About 30% is excreted in the urine and bile as the glucuronide or sulphate conjugate.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Starch Maize

Magnesium Stearate

6.2 Incompatibilities

None.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C

6.3 Nature and contents of container

Pigmented polypropylene container fitted with a tamper evident closure containing 21 or 100 tablets.

Not all pack sizes may be marketed.

6.4 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

UCB Pharma Limited

208 Bath Road,

Slough, Berkshire,

SL1 3WE

UK

8 MARKETING AUTHORISATION NUMBER

PL 00039/0548

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 June 2003

Date of latest renewal: 4 July 2005

10 DATE OF REVISION OF THE TEXT

24/08/2020