SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fematab 1 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains estradiol hemihydrate equivalent to 1 mg estradiol per tablet.

Excipients - Contains Lactose Monohydrate 119.1mg

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Round, biconvex, white film-coated tablet with inscription “379” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women at least 6 months 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)

Older people
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.

The initial daily dosage is 1 mg. The dosage may be increased to 2 mg if required. 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.

Treatment of hysterectomised women and postmenopausal women may be started on any convenient day.

If the patient is menstruating, treatment is started on day one of bleeding.

In women with a uterus, a progestagen should be added to Fematab for 12-14 days each month/28 day cycle.

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

If a dose has been forgotten, it should be taken as soon as possible. If more than 12 hours have elapsed, treatment should be continued with the next tablet without taking the forgotten tablet. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

Method of administration

For oral use.

Fematab can be taken with or without food.

Paediatric Population
There is no relevant indication for the use of Fematab in the paediatric population.

4.3 Contraindications

-Known hypersensitivity to the active substance or to any of the excipients (see section 6.1)
-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 vein 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
-Porphyria

4.4 Special warnings and special 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 Fematab, 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 in cases where 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 progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women can prevent the excess risk associated with oestrogen-only HRT.

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

Breakthrough bleeding and spotting may occur during the first few 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 progestagens 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-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.

HRT, especially oestrogen-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 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 > 30 kg/m2), 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, dyspnea).

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-progestagen or oestrogen-only HRT.

Combined oestrogen-progestagen therapy
The relative risk of CAD during use of combined oestrogen+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 oestrogen+progestagen 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-progestagen 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).

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.

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 oestrogen therapy in this condition.
- Exogenous oestrogens 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 biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- 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 oestrogen-only HRT after the age of 65.
- 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

No interaction studies have been performed.

The efficacy of oestrogens might be impaired:
- The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes 2B6, 3A4, 3A5,

3A7, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamezapine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).
- Ritonavir and nelfinavir, although known as strong inhibitors of CYP450 3A4, A5, A7, 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 via the CYP450 3A4 pathway.
- 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).

Oestrogens might interfere with the metabolism of other drugs:
Oestrogens per se may inhibit CYP450 drug-metabolising enzymes via competitive inhibition. This is in particular to be considered for substrates with a narrow therapeutic index, such as
• tacrolimus and cyclosporine A (CYP450 3A4, 3A3)
• fentanyl (CYP450 3A4)
• theophylline (CYP450 1A2).
Clinically this may lead to an increased plasma level of the affected substances up to toxic concentrations. Thus, careful drug monitoring for an extended period of time might be indicated and a dosage decrease of tacrolimus, fentanyl, cyclosporin A, and theophylline may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy
Fematab is not indicated during pregnancy. If pregnancy occurs during medication with Fematab, 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:
Fematab is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Fematab has no or negligible influence on the ability to drive or use machines

4.8 Undesirable effects

Serious undesirable effects associated with the use of hormone replacement therapy are also mentioned in section “Special warnings and precautions for use”

The table below reports undesirable effects that have been reported in users of hormone replacement therapy (HRT) by MedDRA system organ classes (MedDRA SOCs)

MedDRA system organ class	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000
Infections and manifestations		Vaginal candidiasis	
Immune system disorders		Hypersensitivity	
Metabolism and nutrition disorders	Weight increased, Weight decreased		
Psychiatric disorders		Depressed mood	Anxiety, Libido decreased, Libido increased
Nervous system disorders	Headache	Dizziness	Migraine
Eye disorders		Visual disturbances	Contact lens intolerance
Cardiac disorders		Palpitations	
Gastrointestinal disorders	Abdominal pain, Nausea	Dyspepsia	Bloating, Vomiting
Hepatobiliary disorders		Gall bladder disorder	
Skin and subcutaneous tissue disorders	Rash, Pruritus	Erythema nodosum, Urticaria	Hirsutism, Acne
Musculoskeletal and connective tissue disorders			Muscle cramps
Reproductive system and breast disorders	Metrorrhagia, uterine/vaginal bleeding including spotting	Breast pain, Breast tenderness	Dysmenorrhoea, Vaginal discharge, Premenstrual syndrome, Breast enlargement
General disorders and administration site reactions		Oedema	Fatigue

Other adverse reactions have been reported in association with estradiol treatment (frequency unknown):

<u>Neoplasms benign, and malignant, and unspecified (incl. cysts and polyps):</u>
Breast cancer [a]
Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer [b], ovarian cancer [c]
Increase in size of leiomyoma

<u>Nervous system disorders:</u>

Exacerbation of epilepsy
Probable dementia over the age of 65 (see section 4.4)
Chorea

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 section 4.3 and 4.4.

Gastrointestinal disorders:
Pancreatitis (in women with pre-existing hypertriglyceridemia)
Gastroesophageal reflux disease
Hepatobiliary disorders:
Hepatic function abnormal, sometimes with jaundice

Skin and subcutaneous tissue disorders:
Angioedema,
Erythema multiforme,
Vascular purpura,
Chloasma

Renal and urinary disorders:
Urinary incontinence

Reproductive system and breast disorders:
Fibrocystic breast disease

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

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/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-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 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.			

[b] *Endometrial cancer risk*

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

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

[c] *Ovarian cancer*

Use of oestrogen-only or combined oestrogen-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.

[d] *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:

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

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users
Oral oestrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3 - 10)
Oral combined oestrogen-progestagen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 - 13)

* Study in women with no uterus

[e] *Myocardial infarction*
The risk of coronary artery disease is slightly increased in users of combined oestrogen progestagen HRT over the age of 60 (see section4.4)

[f] *Risk of ischaemic stroke*
The use of oestrogen-only and oestrogen + progestagen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.
This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.4).

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

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users 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 HPRA Pharmacovigilance, Website: www.hpra.ie

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: G03 CA03

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.

Clinical trial information
Relief of oestrogen-deficiency symptoms and bleeding patterns
Relief of menopausal symptoms was achieved during the first few weeks of treatment
Hot flushes have been shown to be significantly reduced with 1mg and 2mg 17 beta estradiol at 4 weeks.

Prevention of osteoporosis

- Oestrogen deficiency at menopause is associated with an increase in bone turnover and a decline in bone mass.
- The effect of oestrogens on 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-analysis of 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 1mg 17 beta estradiol, the mean percentage increase from baseline in lumbar spine bone mineral density (BMD) was 2.7% (C.I: 1.6 to 3.7%) and the mean difference from placebo was 5%. The mean percentage increase from baseline was 1.6% at the femoral neck and 2.6% at the Femoral trochanter.
After 18 months treatment, the placebo group spinal trabecular bone density decreased 4.9% annually ($p < 0.001$), whereas in those taking micronized 17 beta-estradiol bone density tended to increase (annual increases of 1.8% in the 1.0mg micronized 17 beta-estradiol group ($P < 0.001$ vs. placebo).

5.2 Pharmacokinetic properties

Estradiol, estra-1,3,5(10)-triene-3, 17β-diol is identical to human ovarian estradiol. Following oral administration, micronized estradiol is quickly and efficiently absorbed, and extensively metabolised. The major unconjugated and conjugated metabolites are estrone and estrone sulphate, which are the most abundant circulating oestrogens in postmenopausal women. These metabolites can contribute to the estrogenic activity, either directly or after conversion to estradiol. The steady-state pharmacokinetic data of three analytes (i.e. estradiol, estrone and estrone sulphate) after oral administration of micronized estradiol were obtained in studies with healthy postmenopausal women.

Absorption
Absorption of estradiol is dependent on the particle size: micronized estradiol is quickly and efficiently absorbed from the gastro-intestinal tract.

The following table provides the arithmetic mean steady state pharmacokinetic parameters of estradiol (E2), estrone (E1) and estrone sulphate (E1S) for 1mg dose of micronized estradiol. Data is presented as arithmetic mean (standard deviation)

Estradiol 1mg				
Parameters	E2	E1	Parameters	E1S*
C_{max} (pg/mL)	48 (17)	349 (129)	C_{max} (ng/mL)	10.5 (5.6)
C_{min} (pg/mL)	20.8 (11.7)	146 (75)	C_{min} (ng/mL)	2.510 (1.985)
C_{av} (pg/mL)	31.8 (15.3)	231 (106)	C_{av} (ng/mL)	5.280 (3.282)
AUC $_{0-24}$ (pg.h/mL)	751 (331)	5487 (2476)	AUC $_{0-24}$ (ng.h/mL)	129.0 (77.8)

Distribution
Oestrogens can be found either unbound or bound. About 98-99% of the estradiol dose binds to plasma proteins, from which about 30-52% to albumin and about 46-69% to the sex hormone-binding globulin (SHBG).

Biotransformation
Following oral administration, estradiol is extensively metabolised. The major unconjugated and conjugated metabolites are estrone and estrone sulphate. These metabolites can contribute to the oestrogen activity, either directly or after conversion to estradiol. Estrone sulphate may undergo enterohepatic circulation.

Elimination
In urine, the major compounds are the glucuronides of estrone and estradiol. The elimination half-life of estradiol and its main metabolites is between 10-16 h.

Oestrogens are secreted in the milk of nursing mothers.

Linearity/non-linearity
The mean estradiol exposure (i.e. AUC $_{0-24}$ and C_{av}) at steady-state after oral daily dosing of 2mg micronized estradiol is approximately 2-fold greater than that after daily dosing of 1mg micronized estradiol. Based on the elimination half-life of the micronized estradiol, it can be estimated that estradiol concentrations reached steady-stage approximately within one week following oral daily administration.

5.3 Preclinical safety data

There are no preclinical safety data of relevant to the prescriber in the target population that are additional to those already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose
Maize starch
Colloidal anhydrous silica
Magnesium stearate

Opadry coating containing:
Macrogol 400
Titanium dioxide (E171)
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The tablets are packed in blister strips of 28. The blister strip is made of PVC film with a covering aluminium foil. Each carton contains 28 tablets.

6.6 Special precautions for disposal and other handling

Medicines no longer required should not be disposed of via wastewater or household waste. Any unused product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

Thermax Ireland Ltd.
3rd Floor Kilmore House
Park Lane Spencer Dock
Dublin 1
D01 YE64
Ireland

8. MARKETING AUTHORISATION NUMBER

PA22668/015/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 April 1999
Date of last renewal: 16 April 2009

10. DATE OF REVISION OF THE TEXT

May 2025