For the use of a Registered Medical Practitioner Only

1. GENERIC NAME AND BRAND NAME

Estradiol Tablets USP 1 mg
Estrabet™ 1

Estradiol Tablets USP 2 mg
Estrabet™ 2

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Estrabet™ 1
Each film coated tablet contains
Estradiol Hemihydrate I.P.
Equivalent to Anhydrous Estradiol…….1 mg
Colour: Titanium Dioxide I.P.

Estrabet™ 2
Each film coated tablet contains
Estradiol Hemihydrate I.P.
Equivalent to Anhydrous Estradiol…….2 mg
Colour: Titanium Dioxide I.P. and Lake Erythrosine

3. DOSAGE FORM AND STRENGTH
Refer section 1 & 2

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION:
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.
Older People:
The experience treating women older than 65 years is limited.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
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 Warnings and Precautions) should be used.

Treatment of hysterectomized 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 progestogen should be added to estradiol for 12-14 days each month/28 day cycle.
Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomized 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.
Estrabet can be taken irrespective of food.

Paediatric population:
There is no relevant indication for the use of Estrabet in the paediatric population.

4.3 CONTRAINDICATIONS

- Known hypersensitivity to the active substance or to any of the excipients
- Non-hysterectomized women without opposing progestogen
- 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 Warnings and Precautions)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease, as long as the liver function tests have failed to return to normal
- 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.

<u>Medical examination/follow-up</u>

Before initiating or re-instituting 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 checkups 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 estradiol, 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 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 Adverse Reactions). 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 can prevent 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.

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.
Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough 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 suggests an increased risk of breast cancer in women taking combined oestrogen-progestogen and possibly also 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 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 Adverse Reactions).

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 substantially lower than that found in users of oestrogen-progestogen combinations (see section Adverse Reactions).

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

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 of Adverse Reactions in women taking oestrogen-only combined oestrogen-progesterone 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 Adverse Reactions).

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 Adverse Reactions).
• 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 Contraindications).
• 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 oestrogenprogestogen 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 Adverse Reactions).

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 radioimmunoassay) 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-hormonebinding 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).

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 (tablets).

<u>ALT elevations</u>
During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinyl estradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinyl estradiol, such as estradiol, 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 combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. (See section 4.5).

4.5 DRUG INTERACTIONS

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, carbamazepine, phenytoin) 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 regime ombitasvir/paritaprevir/ritonavir with and without dasabuvir, 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. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, 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 combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (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 a plasma increase of the affected substances up to toxic levels. 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 USE IN SPECIAL POPULATION
PREGNANCY AND LACTATION

Pregnancy

Estradiol is not indicated during pregnancy. If pregnancy occurs during medication with estradiol treatment should be withdrawn immediately.

Lactation

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to oestrogens indicate no teratogenic or fetotoxic effect.
Estradiol is not indicated during lactation.

Paediatric population:
The safety and effectiveness of estradiol hemihydrate in paediatric population has not been established and is not indicated for use in children

Geriatric population:
The experience treating women older than 65 years is limited

4.7 EFFECT ON ABILITY TO DRIVE AND USE MACHINES
Estradiol has no or negligible influence on the ability to drive and use machines

4.8 UNDESIRABLE EFFECTS
Serious adverse Reactions associated with the use of hormone replacement therapy are also mentioned in section 4.4.

The table below reports adverse Reactions, 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 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**
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
Skin and subcutaneous tissue disorders	Rash, pruritus	Erythema nodosum, urticaria	Hirsutism, acne
Musculoskeletal and connective tissue disorders			Muscle cramps
Reproductive system and breast disorders	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:
Infections and infestations
Vaginal candidiasis

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

Immune system disorders
Systemic lupus erythematosus

Metabolism and nutrition disorders
Change in carbohydrate metabolism
Hypertriglyceridaemia

Psychiatric disorders
Depression

Nervous system disorders

Probable dementia over the age of 65 (see section Warnings and Precautions), chorea, exacerbation of epilepsy.

Eye disorders
Steepening of corneal curvature

Cardiac disorders
Myocardial infarction [e]

Vascular disorders
Stroke [f]
Arterial thromboembolism. For further information see sections Contraindications and Warnings and Precautions.
Venous thromboembolism[d], i.e. deep leg or pelvic venous thrombosis and pulmonary embolism. For further information see sections Contraindications and Warnings and Precautions).

Gastrointestinal disorders
Pancreatitis (in women with pre-existing hypertriglyceridaemia)
Gastrooesophageal reflux disease

Hepatobiliary disorders
Hepatic function abnormal, sometimes with jaundice, asthenia or malaise, and abdominal pain
Gall bladder disorder

Skin and subcutaneous tissue disorders
Angiooedema
Erythema multiforme, vascular purpura
Chloasma or melasma which may persist when drug is discontinued
Allergic skin reactions
Application site reactions (transdermal administration form (patch))

Renal and urinary disorders
Urinary incontinence
Cystitis-like symptom

Reproductive system and breast disorders
Metrorrhagia, change in cervical erosion
Fibrocystic breast disease

Congenital, familial and genetic disorders
Aggravation of porphyria

Investigations
Total thyroid hormones increased

[a] 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.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section Warnings and Precautions).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period[1]	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
		Oestrogen only HRT	
50-65	9-12	1.2	1-2 (0-3)
		Combined oestrogen-progestogen	
50-65	9-12	1.7	6 (5-7)
[1]Taken from baseline incidence rates in developed countries			
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use 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)[2]
		CEE+MPA oestrogen & progestogen‡	
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)
[2] 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 Warnings and Precautions).

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 the risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

[c] Ovarian cancer risk
Use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 'Warnings and Precaution'). 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 2000users. 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 Warnings and Precautions). 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 & 95%CI	Additional cases per 1000 HRT users
Oral- oestrogen-only[3]			
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)
[3]Study in women with no uterus			

[e] Risk of coronary artery disease
The risk of coronary artery disease is slightly increased in users of combined oestrogenprogestogen HRT over the age of 60 (see section Warnings and Precautions).

[f] 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 Warnings and Precautions.)

WHI studies combined - Additional risk of ischaemic stroke[4] over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1 - 1.6)	3 (1-5)
[4] No differentiation was made between ischaemic and haemorrhagic stroke			

4.9 OVERDOSE
Acute toxicity studies did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose.

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.

5.0 PHARMACOLOGIC PROPERTIES
5.1 Mechanism of action
Estradiol is considerably more potent than estrone and estriol at the estrogen receptor (ER). As a result, the higher estrone concentration in postmenopausal population, can cause various undesirable effects. These effects may include hot flashes, chills, vaginal dryness, mood swings, irregular menstruation, and chills, in addition to sleep problems.
Estradiol workings by binding to subtypes of the estrogen receptor: estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). It also exerts potent agonism of G Protein-coupled estrogen receptor (GPER), which is recognized an important regulator of this drug's rapid effects. Once the estrogen receptor has bound to its ligand, it enters the nucleus of the target cell, regulating gene transcription and formation of messenger RNA. This mRNA makes contact with ribosomes producing specific proteins that express the effect of estradiol upon the target cell. Agonism of estrogen receptors increases pro-estrogenic effects, leading to

the relief of vasomotor and urogenital symptoms of a postmenopausal or low estradiol state.

5.2 Pharmacodynamic Properties

The active ingredient, 17β-estradiol, is chemically and biologically identical to the 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 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.

Estradiol 1 mg:

- 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 1.0 mg micronized 17 betaestradiol group ($p < 0.001$ vs. placebo).

Estradiol 2 mg:

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 1.0 mg micronized 17 beta estradiol group ($p < 0.001$ vs. placebo), and 2.5% in the 2.0 mg micronized 17 betaestradiol group ($p < 0.001$ vs. placebo).

5.3 Pharmacokinetic Properties

Estradiol, estra-1,3,5(10)-triene-3,17ß-diol is identical to human ovarian estradiol. Following oral administration, micronized estradiol is quickly and efficiently absorbed, and extensively metabolized. 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 gastrointestinal tract.

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

Estradiol 1 mg				
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)
Cav (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)

Estradiol 2 mg
The following table provides the arithmetic mean steady state pharmacokinetic parameters of estradiol (E2), estrone (E1) and estrone sulphate (E1S) for 2 mg dose of micronized estradiol.
Data is presented as arithmetic mean (standard deviation).

Estradiol 2 mg				
Parameters	E2	E1	Parameters	E1S*
C_{max} (pg/mL)	89 (16)	591 (178)	C_{max} (ng/mL)	25.9 (16.4)
C_{min} (pg/mL)	35.0 (13.4)	208 (102)	C_{min} (ng/mL)	5.7 (5.9)
Cav (pg/mL)	62.9 (15.6)	208 (102)	C_{av} (ng/mL)	13.1 (9.4)
AUC_{0-24} (pg.h/mL)	1486 (374)	9275 (3389)	AUC_{0-24} (ng.h/mL)	307.3 (224.1)

*E1S: data is taken from oral dosing of estradiol 2 mg + dydrogesterone 20 mg (no clinically relevant effects of dydrogesterone on estradiol kinetics are reported).

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 hormonebinding 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. AUC0-24 and Cav) at steady-state after oral daily dosing of 2 mg micronized estradiol is approximately 2-fold greater than that after daily dosing of 1 mg micronized estradiol. Based on the elimination half-life of the micronized estradiol, it can be estimated that estradiol concentrations reach steady-state approximately within one week following oral daily administration.

6. NON-CLINICAL PROPERTIES
6.1 ANIMAL TOXICOLOGY/PHARMACOLOGY
There are no preclinical safety data of relevance to the prescriber in the target population that are additional to those already included in other sections of the prescribing information

7. DESCRIPTION
Estrabet 1:
ESTRABET 1 is supplied for oral administration, as a film coated tablet of Estradiol. Each film coated tablet of ESTRABET 1 contains Estradiol Hemihydrate equivalent to Anhydrous Estradiol 1 mg.

Estrabet 2:
ESTRABET 2 is supplied for oral administration, as a film coated tablet of Estradiol. Each film coated tablet of ESTRABET 2 contains Estradiol Hemihydrate equivalent to Anhydrous Estradiol 2 mg.

8. PHARMACEUTICAL PROPERTIES
8.1 INCOMPATIBILITIES
Not applicable

8.2 SHELF LIFE
Refer Pack

8.3 PACKAGING INFORMATION
Refer Pack

8.4 STORAGE CONDITION AND HANDLING INSTRUCTIONS
Refer Pack

9. PATIENT COUNSELING INFORMATION

Patients should not take Estrabet:

- In case of women with intact uterus without opposing progestogen, known, past or suspected history of cancer (eg. Breast cancer or endometrial cancer),
- In case of undiagnosed genital bleeding,
- In case of a previous or current venous thromboembolism, acute liver disease, or a history of liver disease.
- If patient is allergic (hypersensitive) to any of the ingredients of this medicine

Patient should tell the doctor if she is taking or have recently taken any other medicines. This includes medicines obtained without a prescription or herbal medicines. In particular, the following medicines may lower the effect of Estrabet.

- Medicines for fits (epilepsy) such as phenobarbital, carbamazepine, phenytoin
- Medicines for infection such as rifampicin, rifabutin, nevirapine, efavirenz may impair the efficacy of Estrabet.
- Medicines for HIV such as Ritonavir, nelfinavir
- Herbal medicines containing St. John's wort

This medicine prescribed for a particular patient shouldn't be passed on to the others. It may harm them, even if their symptoms are the same.

If any of the side effects gets serious, or if the patient notices any side effects not listed above, the doctor needs to be informed.

10. DETAILS OF MANUFACTURER
Refer Pack for manufacturer details.

Marketed By:
Abbott India Limited,
Angel Space, Lifestyle Bldg. No. D-4,
Gala No. 4 to 10 & 14 to 20 Ground Floor,
107 to 110 & 117 to 120 1st Floor,
207 to 210 & 217 to 220 2nd Floor,
Pimplas, Dist. Thane, Bhiwandi - 421 302,
Maharashtra, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER
Refer Pack for Permission/License details.

12. DATE OF REVISION

Version 9.0, dated 03-Oct-25

For product complaints and queries please write to
webmasterindia@abbott.com

SOURCE:

- *CCDS v11.0 dated 13th Jul 2023*