For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ESTROBUILD

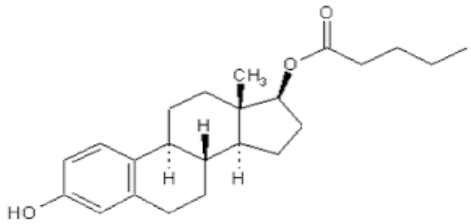
(Estradiol Valerate Tablets 2 mg)

Composition

Each film coated tablet contains:
Estradiol Valerate U.S.P. 2 mg
Excipients q.s.
Colours : Titanium Dioxide I.P. & Lake of Indigo Carmine

PRODUCT DESCRIPTION

Estradiol Valerate is a White, crystalline powder.
Estradiol Valerate is known chemically as Estra-1,3,5(10)-triene-3,17-diol(17β)-, 17-pentanoate.
Molecular formula: $C_{23}H_{32}O_3$, Molecular weight : 356.50
Structural formula:



PHARMACODYNAMICS / PHARMACOKINETICS

Pharmacodynamics

This product contains Estradiol valerate, the valeric-acid ester of the endogenous female oestrogen, estradiol. The active ingredient, synthetic 17 ß-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy. Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women. Evidence from the WHI trial and meta-analysed trials shows that current use of HRT alone or in combination with a progestogen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

Pharmacokinetics

Absorption

After oral administration estradiol valerate is quickly and completely absorbed.

Distribution

Already after 0.5 - 3 hours peak plasma levels of estradiol, the active drug substance, are measured. As a rule, after 6 - 8 hours a second maximum appears, possibly indicating an entero-hepatic circulation of estradiol. In plasma, estradiol is mainly found in its protein-bound form. About 37% are bound to SHBG and 61% to albumin. Cumulation of estradiol after daily

repetitive intake of Estradiol does not need to be expected. The absolute bioavailability of estradiol amounts to 3 - 5% of the oral dose of estradiol valerate.

Metabolism
Esterases in plasma and the liver quickly decompose estradiol valerate into estradiol and valeric acid. Further decomposition of valeric acid through β-oxidation leads to C2-units and result in CO_2 and water as end products. Estradiol itself undergoes several hydroxylating steps. Its metabolites as well as the unchanged substance are finally conjugated. Intermediate products of metabolism are estrone and estriol, which exhibit a weak oestrogenic activity of their own, although this activity is not so pronounced as with estradiol. The plasma concentration of conjugated estrone is about 25 to 30 fold higher than the concentration of unconjugated estrone. In a study using radioactive labelled estradiol valerate about 20% of radioactive substances in the plasma could be characterised as unconjugated steroids, 17% as glucuronized steroids and 33% as steroid sulphates. About 30% of all substances could not be extracted from the aqueous phase and, therefore, probably represent metabolites of high polarity.

Excretion
Estradiol and its metabolites are mainly excreted by the kidneys (relation of urine:faeces = 9:1). Within 5 days about 78 - 96% of the administered dose is excreted with an excretion half-life of about 27 hours.

INDICATION
Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in peri- and postmenopausal women. 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.

RECOMMENDED DOSAGE AND MODE OF ADMINISTRATION
Estradiol is an oestrogen-only product.
One tablet of Estradiol to be taken daily. It does not matter at what time of day the woman takes her tablet, but once she has selected a particular time she should keep to it every day. Treatment is continuous, which means that the next pack follows immediately without a break. For initiation and continuation of treatment of menopausal symptoms, the lowest effective dose for the shortest duration should be used. Treatment to control menopausal symptoms should be initiated with Estradiol 1mg. If considered necessary, Estradiol 2mg should be used. Once treatment is established the lowest effective dose necessary for relief of symptoms should be used. For prevention of postmenopausal osteoporosis one tablet of Estradiol 2mg is to be taken daily. In women with an intact uterus, a progestogen should be added to Estradiol for at least 12 - 14 days each month. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

How to start Estradiol 2mg
If the woman has an intact uterus and is still menstruating, a combination regimen with Estradiol and a progestogen, commencing with the oestrogen phase, should begin on the first day of bleeding. If the menstrual periods are very infrequent or if amenorrhoea is established, she may start at any time provided, if appropriate, pregnancy has been excluded. In women transferring

from a continuous combined HRT product, treatment with Estradiol may be started on any day. In women transferring from cyclic or continuous sequential HRT regimens, the woman should complete the cycle and then change to Estradiol without a break in therapy.

Missed or lost tablets
If the woman forgets to take a tablet at the usual time, she may take it within the following 12 hours. If the woman is more than 12 hours late the forgotten tablet should not be taken and the remaining tablets taken at the usual time on the right days. A missed dose may lead to breakthrough bleeding or spotting.

Children
Not recommended for children

CONTRAINDICATIONS
- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours e.g. endometrial cancer
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Severe renal disease
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency)
- 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
- Known hypersensitivity to the active substances or to any of the excipients

WARNINGS AND PRECAUTIONS
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 risk and benefits should be undertaken at least annually and HRT should only be continued as long as the 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. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision:
If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely

supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Estradiol valerate, in particular:
- endometriosis,
- risk factors for thromboembolic disorders,
- 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 (SLE),
- a history of endometrial hyperplasia,
- 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.

Endometriosis and carcinoma
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 suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also 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 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 years.

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-progestagen combinations.

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-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism
HRT is associated with a 1.3 -to 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.

Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (Body Mass Index >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.

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. Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

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 four to six 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.

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

Coronary artery disease (CAD)
There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-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.

Ovarian Cancer
Ovarian cancer is much rarer than breast cancer. Long-term (at least 5 to 10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer.

Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller, risk.

Other conditions
Oestrogens 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 Estradiol is increased.

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.

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-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).

Thyroid function should be monitored regularly in patients who require thyroid hormone replacement therapy and who are also taking oestrogen in order to ensure that thyroid hormone levels remain within an acceptable range.

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.

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

Patients with rare hereditary problems of galactose intolerance, of Lapp lactase deficiency or of glucose-galactose malabsorption should not take this medicine.

INTERACTIONS WITH OTHER MEDICAMENTS

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

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Herbal preparations containing St John's wort (Hypericum perforatum) may induce the metabolism of oestrogens.

Some laboratory tests may be influenced by oestrogen therapy, such as tests for glucose tolerance or thyroid function.

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

Pregnancy

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

The result of most epidemiological studies to date relevant to inadvertant foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

Lactation

Estradiol is not indicated during lactation.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS

The following undesirable effects have been reported in users of Estradiol and other oral HRT preparations.

Neoplasms benign, malignant and unspecified

Breast cancer*, Endometrial cancer*

Immune system disorders

Hypersensitivity reaction, Exacerbation of hereditary angioedema

Metabolism and nutrition disorder

Porphyria aggravated, Increased or decreased weight, increased appetite, Carbohydrate tolerance decreased

Psychiatric disorders
Anxiety/depressive symptoms, Decreased or increased libido
Nervous system disorders
Migraine, Headache, Dizziness, Fatigue, Chorea, Stroke*
Eye disorders
Visual disturbances, Intolerance to contact lenses
Cardiac disorders
Palpitations, Myocardial infarction*
Vascular disorders
Hypertension, Thrombophlebitis, Venous Thromboembolism*
Respiratory, thoracic and mediastinal disorders
Epistaxis
Gastrointestinal disorders
Dyspepsia, Abdominal pain, Vomiting, Nausea, Bloating, Flatulence
Hepatobiliary disorders
Gall bladder disease including Cholestasis
Skin and subcutaneous tissue disorders
Rashes, various Skin disorders (including Pruritus, Eczema, Urticaria, Acne, Hirsutism, Hair loss, Erythema nodosum, Erythema multiforme, Rash hemorrhagic, Chloasma
Musculoskeletal and connective tissue disorders
Muscle cramps, Leg pain
Renal and urinary disorders
Cystitis-like symptom
Reproductive system and breast disorders
Increased size of uterine fibroids, Vaginal candidosis, Uterine cervical erosions, Changes in vaginal bleeding pattern and abnormal bleeding or flow, Breakthrough bleeding, Spotting (bleeding irregularities usually subside during continued treatment), Dysmenorrhoea, Changes in vaginal secretion, Premenstrual-like syndrome, Breast secretion, Breast tenderness, enlargement or pain.
General disorders and administration site conditions
Oedema
* Please see further information below.

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.
Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations. The level of risk is dependent on the duration of use. 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 of use:

Age range (years)	**Additional cases per 1000 never-users of HRT over[a] 5 year period[a]**	**Risk ratio & 95% CI[b]**	**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-progestagen			
50-65	9-12	1.7	6(5-7)

[a] Taken from baseline incidences in developed countries.
[b] Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.

US WHI studies - additional risk of breast cancer after 5 years of 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)[a]
CEE + MPA oestrogen & progestagen[b]			
50-79	14	1.2(1.0-1.5)	+4(0-9)

[a] WHI study in women with no uterus, which did not show an increased in risk of breast cancer.
[b] When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1000 women with an 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. 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 risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

Risk of venous thromboembolism

HRT is associated with a 1.3 - 3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT. Results of the WHI studies are presented:

WHI Studies - additional risk of VTE over 5 years of 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[a]			
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)
[a] Study in women with no uterus.			

Risk of coronary artery disease
The risk of coronary artery disease is slightly increased in users of combined oestrogen progestagen HRT over the age of 60.

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.

WHI studies combined - Additional risk of ischaemic stroke[a] over 5 years of 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)
[a] No differentiation was made between ischaemic and haemorrhagic stroke.			

Other adverse reactions have been reported in association with oestrogen/progestogen treatment :
- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65
- endometrial hyperplasia
- jaundice cholestatic
- cholelithiasis
- uterine leiomyoma
- liver function test abnormal
- diarrhoea
- migraine
- pain in extremity
- breast tenderness
- dry eyes
- tear film composition changes

OVERDOSE
Nausea and vomiting may occur with an overdose. There are no specific antidotes, and treatment should be symptomatic. Withdrawal bleeding may occur in females with a uterus.

STORAGE
Store protected from light & moisture, at a temperature not exceeding 30^{o}C.

Keep out of reach of children.

EXPIRY DATE
Do not use later than expiry date.

PRESENTATION
Estrobuild is available as blister strip of 28 tablets.

MARKETED BY

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