

UK Prescribing information – Vagirux

Refer to Summary of Product Characteristics for further details.

Product name: Vagirux 10 microgram vaginal tablets.

Composition: Each vaginal tablet contains estradiol hemihydrate equivalent to 10 microgram estradiol.

Indications: Treatment of vaginal atrophy due to estrogen deficiency in postmenopausal women with or without a uterus.

Dosage and administration: Treat vaginal infections prior to starting Vagirux therapy.

Start treatment on any convenient day.

In women with or without a uterus:

Initial dose: One vaginal tablet daily for two weeks.

Maintenance dose: One vaginal tablet twice a week.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used.

Systemic exposure to estrogen remains within the normal postmenopausal range following administration of Vagirux vaginal tablet and so it is not recommended to add a progestogen.

Missed dose: A missed dose should be taken as soon as remembered. A double dose should be avoided.

Method of administration: Vagirux is administered intravaginally by use of a reusable applicator. See SmPC for full instructions on how to administer.

Contraindications: Known, past or suspected breast cancer. Known or suspected estrogen-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). 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. Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions: HRT for menopausal symptoms should only be initiated for those that adversely affect quality of life. Assess the risks and benefits at least annually and continue HRT only as long as benefit outweighs risk. *Medical examination/follow-up:* Before initiating or reinstating HRT, a complete personal and family medical history should be obtained. 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 in accordance with currently accepted screening practices and 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. The pharmacokinetic profile of Vagirux shows that there is very low systemic absorption of estradiol during treatment, however, being an HRT product the following need to be considered, especially for long-term or repeated use of this product. *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 estrogen treatment, in

particular: leiomyoma (uterine fibroids) or endometriosis; risk factors for thromboembolic disorders; risk factors for estrogen-dependent tumours, e.g. first-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; history of endometrial hyperplasia; epilepsy; asthma; otosclerosis. Due to the very low systemic absorption of estradiol during Vagirux treatment, recurrence or aggravation of the above-mentioned conditions is less likely than with systemic estrogen treatment. Reasons for immediate withdrawal of therapy: Discontinue therapy if a contraindication 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: Women with an intact uterus with abnormal bleeding of unknown aetiology or women with an intact uterus who have previously been treated with unopposed estrogens should be examined with special care in order to exclude hyperstimulation/malignancy of the endometrium before initiation of treatment. In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. For vaginally administered estrogen products where the systemic exposure to estrogen remains within the normal postmenopausal range, it is not recommended to add a progestagen. During estradiol 10 microgram vaginal tablets treatment, a minor degree of systemic absorption may occur in some patients, especially during the first two weeks of once-daily administration; however, daily average plasma E₂ concentrations remained within the normal postmenopausal range. Endometrial safety of long-term (more than one year) or repeated use of local vaginally administered estrogen is uncertain. Treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma. If estrogen replacement therapy is prescribed for longer than one year, another physical (including gynaecological) examination should be performed. If bleeding or spotting appears at any time during therapy, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy. The woman should be advised to contact her doctor in case bleeding or spotting occurs during treatment. Unopposed estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis; caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

The following risks have been associated with *systemic* HRT and apply to a lesser extent for vaginally administered estrogen products for which the systemic exposure to the estrogen remains within the normal postmenopausal range. However, they should be considered in case of long term or repeated use of this product.

Breast cancer: The overall evidence suggests an increased risk of breast cancer in women taking combined estrogen-progestagen and possibly also estrogen-only *systemic* HRT, that is dependent on the duration of taking HRT. 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. 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 estrogen-only *systemic* HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Venous thromboembolism: *Systemic* 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. Patients with known thrombophilic states have an increased risk of

VTE and HRT may add to this risk. HRT is contraindicated in such patients. Generally recognised risk factors for VTE include use of estrogens, 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 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. 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, treatment must 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): Randomised controlled data found no increased risk of CAD in hysterectomised women using *systemic* estrogen-only therapy. Ischaemic stroke: *Systemic* estrogen-only therapy is 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 increases with age. Other conditions: Estrogens 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 estrogen replacement or hormone replacement therapy; rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition. Estrogens increase thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, T4 levels or T3 levels. 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). The minimal systemic absorption of estradiol with local vaginal administration is likely to result in less pronounced effects on plasma binding proteins than with systemic treatment. HRT does not improve cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using systemic continuous combined or estrogen-only HRT after the age of 65. 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, the balance of benefits and risks for these women may be more favourable than in older women. Intravaginal applicator may cause minor local trauma, especially in women with serious vaginal atrophy.

Undesirable effects: More than 1100 patients have been treated with estradiol 10 micrograms vaginal tablets in clinical trials, including over 497 patients treated up to 52 weeks. Estrogen-related adverse events such as breast pain, peripheral oedema and postmenopausal bleedings have been

reported with estradiol 10 micrograms vaginal tablets at very low rates, similar to placebo, but if they occur, they are most likely present only at the beginning of the treatment.

Common ($\geq 1/100$ to $< 1/10$): Headache; abdominal pain; vaginal haemorrhage, vaginal discharge or vaginal discomfort. Uncommon ($\geq 1/1,000$ to $< 1/100$): Vulvovaginal mycotic infection; hot flush.; hypertension; nausea; rash; weight increased. Post-marketing experience: the following have been spontaneously reported for patients being treated with estradiol 25 micrograms vaginal tablets and are considered possibly related to treatment. These spontaneous-reported adverse reactions are Very rare ($< 1/10,000$ patient years): Breast cancer; endometrial cancer; generalised hypersensitivity reactions (e.g. anaphylactic reaction/shock); fluid retention; insomnia; migraine aggravated; deep venous thrombosis; diarrhoea; urticaria; rash erythematous; rash pruritic; genital pruritus; endometrial hyperplasia; vaginal irritation; vaginal pain; vaginismus; vaginal ulceration; drug ineffective; weight increased; blood estrogen increased. Other adverse reactions reported in association with systemic estrogen/progestagen treatment: Gall bladder disease; chloasma; erythema multiforme; erythema nodosum; vascular purpura; probable dementia over the age of 65. **Consult summary of product characteristics for detailed information on breast cancer, endometrial cancer, ovarian cancer, venous thromboembolism and ischaemic stroke.**

Packs and NHS Price: Vagirux 24 vaginal tablet pack - £11.34

Legal Classification: POM.

MA Number: PL 04854/0184

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store
Adverse events should also be reported to Gedeon Richter (UK) Ltd on +44 (0) 207 604 8806 or drugsafety.uk@gedeonrichter.eu