Prescribing information – Lenzetto

Refer to Summary of Product Characteristics for further details.

Product name: Lenzetto 1.53 mg/spray, transdermal spray, solution.

Composition: Each spray delivers 90 microliter of transdermal spray, solution containing 1.53 mg of estradiol (equivalent to 1.58 mg of estradiol hemihydrate).

Indications: Hormone Replacement Therapy (HRT) for estrogen deficiency symptoms in postmenopausal women (in women at least 6 months since last menses or surgical menopause, with or without a uterus). The experience in treating women older than 65 years is limited.

Dosage and administration: Starting dose is one metered-dose spray is administered once daily to the dry and healthy skin of the forearm as a starting dose; this may be increased to two metered-dose sprays daily based on clinical response and only after at least 4 weeks of continuous treatment with Lenzetto. The maximum daily dose is 3 metered-dose sprays (4.59 mg/day) to the forearm. Dose increase should be discussed with the physician. For patients who have difficulty applying the prescribed dose to distinct, non-overlapping areas of the same forearm, Lenzetto may also be applied to the alternate forearm or the inner thigh. The lowest effective dose for the shortest duration should be used; when menopausal symptoms are not reduced after a dose increase, the patient should be back-titrated to the previous dose. Re-evaluate continued need for treatment periodically (e.g. 3-month to 6-month intervals). *In women with a uterus:* Lenzetto should be combined with a progestagen approved for addition to estrogen treatment in a continuous - sequential dosing scheme: the estrogen is dosed continuously and progestagen added for at least 12 to 14 days of every 28-day cycle, in a sequential manner. In the combined estrogen- progestogen phase, withdrawal bleeding can occur. A new 28-day treatment cycle is started without a break. *In women without a uterus:* Unless there is a previous diagnosis of endometriosis, it is not recommended to add progestagen for women without a uterus. *Overweight and obese women:* The rate and extent of absorption of Lenzetto can be reduced in overweight and obese women necessitating dose adjustment which should be discussed with the physician. *Paediatric population:* There is no relevant use of Lenzetto in the paediatric population. *Missed dose:* A missed dose should be taken as soon as remembered unless it is almost time for the next dose; the following dose is taken at the usual time. If one or more doses are missed one primer spraying with the cover on is needed. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting. *Method of administration:* Hold container upright and vertical for spraying. Before a new applicator is used for the first time, prime the pump by spraying three times into the cover. If two or three sprays are prescribed as the daily dose, they should be applied to adjacent non-overlapping (side-by-side) 20 cm^2 areas on the inner surface of the arm between the elbow and the wrist and allowed to dry for approximately 2 minutes. Cover the application site with clothing if another person may come into contact with that area of skin after the spray dries. Do not wash the application site or allow another person to touch the site of application within 60 minutes of application. Do not allow children to come in contact with the area of the arm where Lenzetto was sprayed. If this occurs, wash the child's skin with soap and water as soon as possible. Do not allow pets to lick or touch the arm where Lenzetto was sprayed. Small pets may be especially sensitive to the estrogen in Lenzetto. Contact a veterinarian if your pet exhibits mammary/nipple enlargement and/or vulvar swelling, or any other sign of illness. Use within 56 days of first use.

Elevated skin temperature: Clinically relevant changes in absorption of Lenzetto have not been demonstrated with increased ambient temperatures; however, use with caution in extreme temperature conditions, such as sun bathing or sauna. *Application of sunscreen:* When sunscreen is applied about one hour following Lenzetto, estradiol absorption may be decreased by 10%; when sunscreen was applied about one hour prior to Lenzetto, no effect on absorption was observed.

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 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 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. *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 Lenzetto, 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. 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: In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined estrogen–progestagen therapy in non-hysterectomised women prevents the excess risk associated with estrogen-only HRT. 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. Unopposed estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestagens to estrogen 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 estrogen-progestagen and possibly also estrogen-only HRT, that is dependent on the duration of taking HRT. Ovarian cancer: Epidemiological evidence suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestagen HRT. 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. HRT is contraindicated in patients with known thrombophilic states. Generally recognised risk factors for VTE include, use of estrogens, 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. 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, Lenzetto 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): There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestagen or estrogen-only HRT. Ischaemic stroke: Combined estrogen-progestagen and estrogen-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. Visual abnormalities: Retinal vascular thrombosis has been reported in women receiving estrogens. Medication must be discontinued immediately, pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued. Other conditions: Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Closely monitor women with pre-existing hypertriglyceridemia 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. There is some evidence of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65. Alcohol based products are flammable: Avoid fire, flame or smoking until the spray has dried. Paediatric population: Post-marketing reports of breast budding and breast masses in prepubertal females, precocious puberty and gynaecomastia and breast masses in prepubertal males following unintentional secondary exposure to Lenzetto have been reported. In most cases, the condition resolved with removal of Lenzetto exposure. Consideration should be given to discontinuing Lenzetto if conditions for safe use cannot be met.

Undesirable effects: Common (≥1/100 to <1/10): Headache; abdominal pain; nausea; rash; pruritus; breast pain; breast tenderness; uterine/vaginal bleeding including spotting; metrorrhagia; weight increased; weight decreased. Uncommon (≥1/1,000 to <1/100): Hypersensitivity reaction; depressed mood; insomnia; dizziness; visual disturbances; vertigo; palpitations; hypertension; diarrhoea; dyspepsia; erythema nodosum ; urticaria; skin irritation ; myalgia ; breast discolouration ; breast discharge ; cervical polyp ; endometrial hyperplasia ; ovarian cyst ; vaginitis ; oedema ; axillary pain ; gamma-glutamyltransferase increased; blood cholesterol increased. Rare (≥1/10,000 to <1/1,000): Anxiety; libido decreased; libido increased; migraine; contact lens intolerance; bloating; vomiting; hirsutism; acne; muscle spasms; dysmenorrhoea; premenstrual-like syndrome; breast enlargement; fatigue. Frequency not known: Alopecia, chloasma, skin discolouration. **Consult summary of product characteristics for detailed information on breast cancer, endometrial cancer, ovarian cancer and venous thromboembolism.**

Packs and NHS Price: Lenzetto 1.53mg/spray x 1 - £6.90 and Lenzetto 1.53mg/spray x 3 - £20.70

Legal Classification: POM.

MA Number: PL 04854/0130

Marketing Authorisation Holder: Gedeon Richter Plc, Gyömrői út 19-21, 1103 Budapest , Hungary

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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