GEDEON RICHTER

Lenzetto®

Estradiol Metered-Dose Transdermal Spray (Lenzetto®) for the Treatment of Postmenopausal Vasomotor Symptoms

Medicines evidence pack to support formulary and guidelines decision making

For prescribing information, see end of document.

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Lenzetto Overview in Menopausal Therapy

Brand name	Lenzetto
Generic Name	Estradiol 1.53 mg/spray, transdermal spray, solution[1]
Licensed Indication	Hormone Replacement Therapy (HRT) for oestrogen 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.[1]
Anticipated Place in Therapy	Suitable for postmenopausal women requiring hormone replacement therapy for oestrogen deficiency symptoms[1]
Dose	Lenzetto is administered once daily, either as a monotherapy or as a continuous sequential treatment (when combined with a progestogen).[1] One metered-dose spray is administered once daily to the dry and healthy skin of the forearm as a starting dose. The dose may be increased to two metered-dose sprays daily to the forearm based on clinical response. Dose increase should be based on the degree of the woman's menopausal symptoms and should be made 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, may also be applied to sites on the alternate forearm, or to sites on the inner thigh.[1] For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used.[1] When the degree of the woman's menopausal symptoms is not reduced after a dose increase, the patient should be back-titrated to the previous dose.[1] Patients should be re-evaluated periodically as clinically appropriate (e.g. 3-month to 6-month intervals) to determine if treatment is still necessary.[1] When oestrogen is prescribed for a postmenopausal woman with a uterus, a progestagen approved for addition to oestrogen treatment should also be initiated to reduce the risk of endometrial cancer. Only progestagens approved for addition to oestrogen treatment should be administered.[1]

	<u>In women with a uterus</u> In women with an intact uterus, the product should be combined with a progestagen approved for addition to oestrogen treatment in a continuous - sequential dosing scheme: the oestrogen is dosed continuously. The progestagen is added for at least 12 to 14 days of every 28-day cycle, in a sequential manner.[1] Advice on how to initiate treatment should be given for treatment naive patients and for patients changing from other HRTs (cyclic, sequential or continuous combined). In the period in which the oestrogen is combined with the progestagen, a withdrawal bleeding can occur. A new 28-day treatment cycle is started without a break.[1] <u>In women without a uterus</u> Unless there is a previous diagnosis of endometriosis, it is not recommended to add progestagen for women without a uterus.[1]
Administration	The plastic nozzle controls the distance, angle and area of application[2] • No unnecessary contact with the medicine[3] • Low possibility of leakage[3] • Full control over the application[3] The container should be held upright and vertical for spraying. Before a new applicator is used for the first time, the pump should be primed by spraying three times into the cover. The daily dose is one metered-dose spray on the inner forearm. 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. Women should cover the application site with clothing if another person may come into contact with that area of skin after the spray dries. The site of application should not be washed for 60 minutes. Do not allow another person to touch the site of application within 60 minutes of application.[1] Do not allow children to come in contact with the area of the arm where Lenzetto was sprayed. If a child comes in contact with the part of the arm where Lenzetto was sprayed, wash the child's skin with soap and water as soon as possible.[1] Do not allow pets to lick or touch the arm where Lenzetto was sprayed. Small pets may be especially sensitive to the oestrogen in Lenzetto. Contact a veterinarian if your pet exhibits mammary/nipple enlargement and/or vulvar swelling, or any other sign of illness.[1] Studies suggest that compared to applying it to the inner surface of the forearm, absorption of estradiol is similar when Lenzetto is applied to the skin of the thigh, but is lower when applied to the skin of the abdomen.[1] If the product is used according to the instructions, irrespective of different spray shape or pattern on the skin

	each puff will deliver the same amount of ingredient on the skin.[1]
Cost	Lenzetto 1.53mg/spray x 1packs[1] - £6.90[4] Lenzetto 1.53mg/spray x 3packs[1] - £20.70[4] Each pack contains 56 metered-dose sprays.[1]

Lenzetto® is an estradiol metered-dose transdermal spray that has been developed for the treatment of oestrogen deficiency symptoms in postmenopausal women (in women at least 6 months since last menses or surgical menopause, with or without a uterus).[1]

As early as 1998, a small study in four women demonstrated that a metered spray of 17β-estradiol together with a dermal penetration enhancer, was capable of delivering a clinically relevant dose of estradiol in postmenopausal women with once daily dosing. The women received a daily dosage of 17β-estradiol, consisting of three 1 mg metered doses, each applied as a single spray over 10cm^2 of the ventral forearm for 9 days. The authors reported that 'the estradiol/oestrone ratio obtained for the topical aerosol was consistent with those of topical gel and transdermal patch formulations.[5] Lenzetto contains a similar vehicle excipient, designed to affect the absorption of estradiol across the skin.[1] This allows delivery of a low, effective dose of estradiol while minimising local irritation and eliminating the requirement for a skin patch.[5]

Lenzetto has been shown to provide accurate and reproducible delivery of estradiol to the systemic circulation by administration of a rapidly drying spray to a small area of intact skin, typically on the forearm.[1]

Unmet Need

Systemic hormone replacement therapy (HRT) with estradiol administered transdermally provides effective relief from vasomotor symptoms while reducing the adverse effects associated with oral dosing.[6,7,8]

Estradiol administered transdermally provides effective estradiol concentrations in the blood at a much lower dose than is required with oral administration, since estradiol administered transdermally is not subject to metabolic first pass through the liver.[6]

In addition, transdermal estradiol has little or no effect on a number of other factors including, sex hormone binding globulin and C-reactive protein.[6,7,8] NICE guidelines therefore recommend the use of transdermal HRT in patients at an increased risk of stroke or VTE, including those patients with a body mass index (BMI) greater than 30 kg/m^2.[9]

The mode of administration can make a big difference to medicines adherence in women taking HRT to relieve symptoms of the climacteric. Transdermal systemic HRT is dominated by adhesive patches. Clinical trials of transdermal patches have reported skin irritation and sensitivity (including, itching, oedema, rash, and skin pigmentation) in up to 1 in 5 women.[10,11] Application site reactions reported by manufacturers range from 3%[12] to 20.8%.[13]

Lenzetto transdermal spray offers the benefits of the transdermal route of administration, and its metered-dose delivers a controlled amount of estradiol.[1] Also, given the importance of mode of administration in HRT,[2] it provides an additional choice for women seeking treatment for the symptoms of the climacteric.

Introduction

Lenzetto is an estradiol metered-dose transdermal spray that has been developed for the treatment of postmenopausal estrogen deficiency.[1] This spray contains vehicle excipients that improve absorption of estradiol across the skin when compared with sprays containing only estradiol. It was designed to deliver a low, effective dose of estradiol while minimising local irritation, increasing ease of use compared with a gel or cream, and eliminating the requirement for a skin patch.[5]

The Medicines and Healthcare Products Regulatory Agency granted a marketing authorisation valid throughout the European Union for Lenzetto on 13 August 2015. Gedeon Richter UK launched Lenzetto in the UK on 1st April 2020.

Background

Loss of oestrogen secretion from the ovaries in postmenopausal women is associated with a number of uncomfortable vasomotor symptoms, including hot flushes and night sweats.[14] These vasomotor symptoms, which result from dysfunction of central thermoregulatory systems,[15] can be frequent and/or severe in many of women, [14,16] and can impact negatively on their quality of life.[17]

Replacement of oestrogen using hormone replacement therapy (HRT) can significantly reduce vasomotor symptoms, leading to improvements in quality of life in postmenopausal women.[18,19,20]

When administered orally, estradiol is metabolised quickly in the gut wall and liver to the less active metabolite estrone, effectively reducing the biological activity of oral estrogen. However, estradiol administered transdermally provides effective estradiol concentrations in the blood at a much lower dose than is required with oral administration, since estradiol administered transdermally is not subject to metabolic first pass through the liver.[6]

Furthermore, transdermal estradiol has little or no effect on a number of other factors including sex hormone binding globulin and C-reactive protein.[6,7,8]

NICE guidelines therefore recommend the use of transdermal HRT rather than oral in patients at an increased risk of stroke or VTE, including those patients with a body mass index (BMI) greater than 30 kg/m^2.[9]

Current Management

A range of HRTs are offered to women with menopause. The nature and dosage of the HRT that will be prescribed depend on the patient's profile, such as her age or when her menopause started, and also her preference for one formulation over the other ones. Treatment can also be adapted if needed, based on changes in symptoms.[9]

While transdermal delivery of estradiol offers significant benefits over oral dosing for HRT, clinical trials of transdermal patches have reported skin irritation and sensitivity (including, itching,

oedema, rash, and skin pigmentation) in up to 1 in 5 women.[10,11] Application site reactions reported by manufacturers range from 3%[12] to 20.8%.[13]

Alternative transdermal delivery formulations have been developed, including gels and emulsions, which are applied to large surface areas of skin to be treated during administration,[21,22,23] for example the outer arm and shoulder of both arms, or the mid-inner thigh of both legs, or the lower body or thighs. Transdermal sprays, applied to the inner forearm, may offer an alternative transdermal delivery method that addresses some of the side effects or administration issues of oral, gel, patch and emulsion formulations.[2]

Transdermal sprays typically comprise four main constituents: drug, solvent systems, polymers and penetration enhancers.[2] After application, the spray forms a rapid-drying and invisible film over the skin, delivering sustained concentrations of drug over a prolonged period.[2] Transdermal sprays offer multiple benefits to patients, including dose flexibility, cosmetic acceptability and good skin tolerability.[2]

Safety aspects of HRT

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.[1]

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.[1]

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.[1]

Conditions which need supervision[1]

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 (see below)
- Risk factors for oestrogen-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
- A history of endometrial hyperplasia (see below)

- Epilepsy
- Asthma
- Otosclerosis

Women on HRT can experience breast soreness, mood swings, bloating or vaginal bleeding.[1]

Safety concerns with HRTs are summarised below.

Reasons for immediate withdrawal of therapy[1]

Therapy should be discontinued in case 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 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. After stopping treatment, risk may remain elevated for at least 10-years.[1]

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 prevents the excess risk associated with oestrogen-only HRT.[1]

For Lenzetto, the endometrial safety of added progestagens has not been demonstrated.[1]

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.[1]

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.[1]

Breast cancer

Overall, evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestogen, and possibly also oestrogen-only, HRT; this is dependent on the duration of taking HRT.[1]

Combined oestrogen-progestogen therapy

Results from the Women's Health Initiative study (WHI)[24], which was a randomised placebo-controlled trial, and other epidemiological studies, carried out separately, 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.[1]

Oestrogen-only therapy

The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT.[24] 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.[1]

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.[1]

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.[1]
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.[1]
Some other studies, including the WHI trial suggest that the use of combined HRTs may be associated with a similar, or slightly smaller, risk.[1]

Venous thromboembolism

HRT is associated with a 1.3–3 fold risk of developing VTE (deep vein thrombosis or pulmonary embolism). The occurrence of such an event is more likely in the first year of HRT than later.[1]

- 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.[1]
- Generally recognised risk factors for VTE include the 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.[1]
- 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 4–6 weeks earlier is recommended. Treatment should not be restarted until the patient is completely mobilised.[1]
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at a young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).[1]
- Women already on chronic anticoagulant treatment require careful consideration of the risk/benefit of HRT use.[1]
- 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).[1]

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-progestogen or oestrogen-only HRT.[1]

Combined oestrogen-progestogen therapy

The relative risk of CAD during use of combined oestrogen and 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 plus progestogen is very low in healthy women close to menopause, but will rise with more advanced age.[1]

Oestrogen-only therapy

Randomised controlled data showed no increased risk of CAD in hysterectomised women using oestrogen-only therapy.[1]

Ischaemic stroke

Combined oestrogen-progestogen and oestrogen-only therapies are associated with an up to 1.5-fold increase in the 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.[1]

Visual abnormalities

Retinal vascular thrombosis has been reported in women receiving oestrogens. Discontinue medication 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, oestrogens should be permanently discontinued.[1]

Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.[1]

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.[1]

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 radioimmunoassay). T3 resin uptake is decreased, reflecting elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum (e.g. corticoid binding globulin (CBG) and 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).[1]

HRT use does not improve cognitive function. There is some evidence of an increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.[1]

Alcohol based products are flammable

Avoid fire, flame or smoking until the spray has dried.[1]

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.[1]

Elevated skin temperature
The effect of increased ambient temperature has been demonstrated and approximately 10% difference was observed in the absorption of Lenzetto. This effect is not expected to be of clinical relevance for daily administration of Lenzetto. Nevertheless, Lenzetto should be used with caution in extreme temperature conditions, such as sunbathing or sauna.[1]

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.[1]

The possibility of unintentional secondary exposure to Lenzetto should be brought to the attention of a physician. The physician should identify the cause of abnormal sexual development in the child. If unexpected breast development or changes are determined to be the result of unintentional exposure to Lenzetto, the physician should counsel the woman on the appropriate use and handling of Lenzetto when around children. Women should cover the Lenzetto application site with clothing if another person (especially children) may come into contact with the site. Consideration should be given to discontinuing Lenzetto if conditions for safe use cannot be met.[1]

Product Name and Dosage

Lenzetto® 1.53 mg/spray, transdermal spray, solution[1]

Lenzetto is available in a glass vial fitted with a metered dose pump. The unit is encased in a plastic housing with a conical bell opening that controls the distance, angle, and area of application of the metered dose spray.[1]

Each pack contains one container of 8.1 mL transdermal spray solution and is designed to deliver 56 sprays after priming. Each metered-dose spray delivers 1.53 mg of estradiol (equivalent to 1.58 mg of estradiol hemihydrate) to the skin as a 90 microL solution.[1]

Lenzetto contains vehicle excipients associated with the absorption of estradiol across the skin, allowing delivery of a low, effective dose of estradiol while minimising local irritation and eliminating the requirement for a skin patch.[5]

As a starting dose, one metered-dose spray is administered once daily. The dose may be increased up to three metered-dose sprays daily to the forearm based on the clinical response.[1]

The maximum daily dose is three metered-dose sprays (4.59 mg/day). Dose increase should be discussed with the physician and should be based on the degree of the woman's menopausal symptoms. It should be made only after at least four weeks of continuous treatment with Lenzetto.[1]

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used.[1]

When the degree of the woman's menopausal symptoms is not reduced after a dose increase, the patient should be back-titrated to the previous dose.[1]

When oestrogen is prescribed for a postmenopausal woman with a uterus, a progestagen approved for addition to oestrogen treatment should also be initiated to reduce the risk of endometrial cancer. Only progestagens approved for addition to oestrogen treatment should be administered.[1]

Classification

ATC code: G03CA03[1]

Cost

£6.90[4] for 1 container of 8.1 mL transdermal spray solution, designed to deliver 56 sprays after priming. (Triple pack of 3 containers - £20.70)[4]

Estimated Annual Usage: 7 - 20 containers of 8.1 mL transdermal spray solution depending on dose used.[1,25]

Manufacturer & Marketing Authorisation Holder

Manufacturer:[1]

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

Marketing Authorisation Holder:[1]

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

Promoted in the UK by:

Gedeon Richter (UK) Ltd
127 Shirland Road,
London, W9 2EP
United Kingdom

Indication

Lenzetto® is indicated as Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women (in women at least 6 months since last menses or surgical menopause, with or without a uterus).[1]

The experience in treating women older than 65 years is limited.[1]

Pharmacology

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.[1]

Absorption

In a multiple-dose study, postmenopausal women were treated for 14 days with one-, two- or three- 90 microliter sprays of Lenzetto on the inner forearm. Serum concentrations of estradiol appeared to reach a steady state after 7-8 days of application of Lenzetto.
Following morning administration, blood levels remained relatively stable and within the therapeutic range throughout the 24-hour period following administration with peak levels between 2 AM and 6 AM.[1]

Studies suggest that compared to applying it to the inner surface of the forearm, absorption of estradiol is similar when Lenzetto is applied to the skin of the thigh, but is lower when applied to the skin of the abdomen.[1]

In a clinical study, postmenopausal women were treated for 12 weeks with one, two or three 90 microliter sprays of Lenzetto on the inner forearm and blood levels of estradiol were measured at Week 4, 8 and 12. The estradiol exposure increased with increasing dose (one, two, three sprays respectively) but the increase was slightly less than proportional to dose.[1]

Special Populations

Older women: There is limited experience of treating women older than 65 years with Lenzetto.[1]
Women with renal impairment or cardiac dysfunction: Oestrogens may cause fluid retention. Therefore, patients with renal impairment or cardiac dysfunction should be carefully observed.[1]
Women with hypertriglyceridemia: 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.[1]
Overweight and obese women: There is some limited data indicating that the rate and extent of absorption of Lenzetto can be reduced in overweight and obese women, and the dose of Lenzetto may therefore require adjustment in this population during treatment. Dose modification should be discussed with the physician.[1]
Paediatric population: There is no relevant indication for use of Lenzetto in children.[1]

Contraindications[1]

Lenzetto is contraindicated in women with:

- 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).
- 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

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.[1]

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.[1]

Medical examination/follow-up[1]
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[1]
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 (see below)
- - Risk factors for oestrogen-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
- - A history of endometrial hyperplasia (see below)
- - Epilepsy
- - Asthma
- - Otosclerosis

Reasons for immediate withdrawal of therapy[1]
Therapy should be discontinued in case 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

Please refer to Current Management - Safety aspects of HRT (earlier)

Pivotal Trials

Summary table of clinical studies

Table 1: Summary of Lenzetto clinical studies

Study	Design	N	Outcomes
Morton et al., 2009[26]	Single-centre, randomised, open-label, parallel group	72	• Estradiol delivered at therapeutic concentrations • Low levels of the main metabolite estrone
Schumacher et al., 2009[27]	Single-centre, open-label	20	• Estradiol absorption was not affected when sunscreen was applied one hour before administration of the spray. • Application of sunscreen one hour after administration of the spray resulted in a slight decrease in estradiol absorption. • Washing the site of application 1 hour after administration had no significant effect on the systemic absorption of estradiol. • The use of a transdermal estradiol spray did not result in a significant transfer of estradiol by skin-to-skin contact one hour after administration.
Buster et al., 2008[3]	Randomized, double-blind, placebo-controlled, Phase 3	454	• Reduced frequency and severity of vasomotor symptoms versus placebo
Kovács et al., 2016[28,29]	Network Meta - analysis		• Similar efficacy to transdermal patch of equivalent dose based on indirect analysis • Better tolerability profile compared with transdermal patch in application site analysis based on indirect analysis

HRT, hormone replacement therapy; N=number of patients

Study of the pharmacokinetics of Estradiol applied as a transdermal spray, in healthy postmenopausal women[26]

This study was undertaken to evaluate the steady-state pharmacokinetics of estradiol applied as a transdermal spray in 72 healthy postmenopausal women.

Study summary

- Exposure to estradiol and its resulting major metabolites, estrone and estrone sulfate, increased with dose on days 1 through 14.
- Therapeutic levels of estradiol were achieved with the metered-dose estradiol transdermal spray. Serum levels peaked at 18–20 hours after each dose.
- Low serum estrone and estrone sulfate concentrations were observed.
- Estrone/estradiol ratios were comparable to those observed in premenopausal women.

Study design and treatment

This was a single-centre, randomised, open-label, parallel group study. A total of 72 healthy postmenopausal women were randomly assigned in parallel to receive one-, two-, or three-spray doses (24 participants/dose level) of a 1.7% (w/v) estradiol metered-dose transdermal spray (1.53 mg/spray) once daily for 14 days.

The site of application was each participant's inner forearm, and the spray was applied at the same time each day. Multiple doses, if required, were applied at non-overlapping sites on the inner forearm.

Study population

All subjects were healthy, non-smoking, postmenopausal women aged 40–64 years, with serum estradiol levels <25 pg/mL and BMI of 19–32 kg/m^2. They had no abnormal findings at screening and had not been treated with hormonal products for sufficient periods (depending on the route of administration) before the study.

Women with contraindications for oestrogen therapy, skin allergies, history of drug abuse, or who were on hepatic enzyme inducers were excluded.

Study assessments and endpoints

The primary objective was to evaluate the steady-state pharmacokinetics of estradiol, estrone and estrone sulfate following the application of estradiol in the form of a transdermal spray. Safety was also assessed.

Study results

Baseline demographics

A total of 72 women were randomised in the study, and overall demographics and baseline characteristics were well balanced between the study groups (table 2)

Table 2: Overview of baseline characteristics -

Characteristic	1 spray (n=24)	2 sprays (n=24)	3 sprays (n=24)	Total (n=72)
Mean age, years (SD)	55.8 (4.86)	53.9 (4.92)	56.0 (5.81)	55.2 (5.23)
Mean BMI, kg/m^2 (SD)	26.5 (2.84)	26.4 (2.43)	26.3 (2.80)	26.4 (2.66)
Race, n (%)				
Hispanic	22 (91.7)	20 (83.3)	23 (95.8)	65 (90.3)
Black	1 (4.2)	3 (12.5)	0 (0.0)	4 (5.6)
White	1 (4.2)	1 (4.2)	1 (4.2)	3 (4.2)

BMI=body mass index; SD=standard deviation

Steady state pharmacokinetics of estradiol

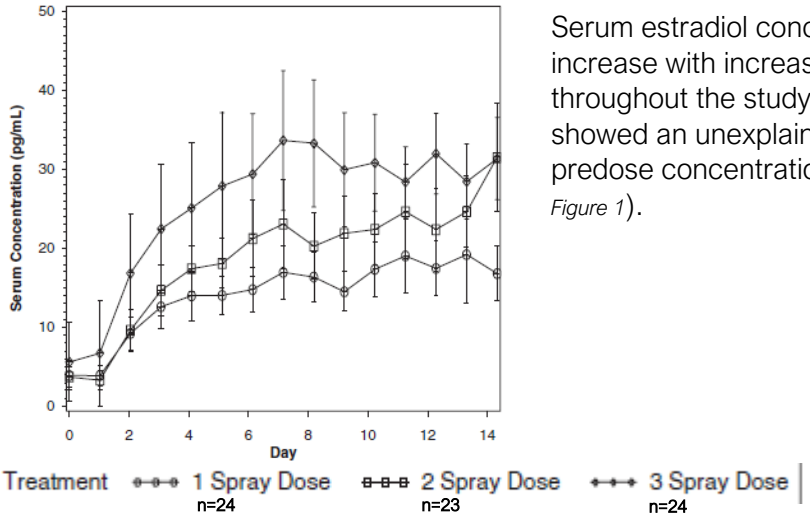
Participants who received two and three 90-µL sprays daily had average trough serum estradiol concentrations of 18.1 and 19.6 pg/mL, respectively; these concentrations are both above the minimum effective serum level. Steady state was reached at days 7–8 following one-, two- or three-spray doses (Table 3).

Table 3: Pharmacokinetic parameters following Day 14 dosing

Parameter[a]	Estradiol			Estrone			Estrone sulfate		
	1 spray (n=24)	2 sprays (n=23)	3 sprays (n=24)	1 spray (n=24)	2 sprays (n=23)	3 sprays (n=24)	1 spray (n=24)	2 sprays (n=23)	3 sprays (n=24)
AUC_{0-24}, pg.h/mL (%)	471 (49)	736 (43)	742 (30)	886 (29)	1208 (26)	1367 (30)	16501 (58)	26515 (45)	27971 (45)
C_{max}, pg/mL (%)	36.4 (62)	57.4 (94)	54.1 (50)	49.6 (34)	60.2 (25)	71.4 (37)	1100 (76)	1543 (47)	1657 (43)
T_{max},h[b]	20 (0–24)	18 (0–24)	20 (0–24)	17 (0–24)	10 (0–24)	10 (0-24)	9 (0–24)	8 (0–24)	10 (0–24)
C_{min}, pg/mL (%)	11.3 (52)	18.1 (51)	19.6 (27)	30.3 (31)	41.0 (29)	46.5 (32)	486 (58)	701 (54)	781 (47)
C_{avg}, pg/mL (%)	19.6 (49)	30.7 (43)	30.9 (30)	36.9 (29)	50.3 (26)	57.0 (30)	688 (58)	1105 (45)	1166 (45)

$AUC_{(0-24)}$= area under the serum concentration-time curve from time 0 through 24 hours; C_{avg}= average concentration; C_{max}, maximum concentration; T_{max}= median time to maximum concentration (minimum–maximum)
[a]Mean (CV%); [b]Median (minimum–maximum)

Figure 1: Mean (± standard error) predose estradiol concentration (Days 0–14)

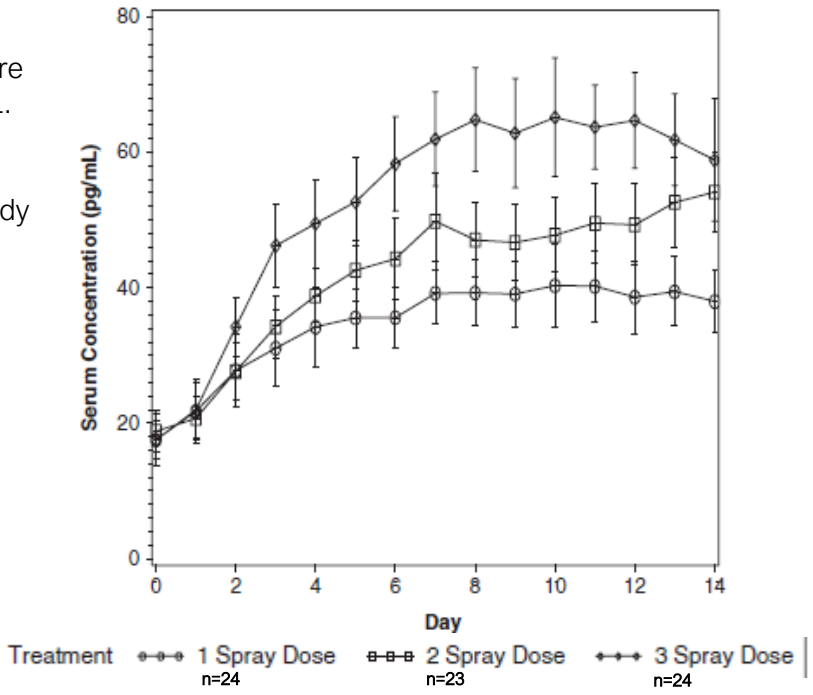


Serum estradiol concentrations appeared to increase with increase in number of sprays throughout the study. The 2-spray group, however, showed an unexplained sharp increase in mean predose concentration just before the last dose (*Figure 1*).

Estrone pharmacokinetics

Figure 2: Mean (± standard error) predose estrone concentrations (Days 0–14)

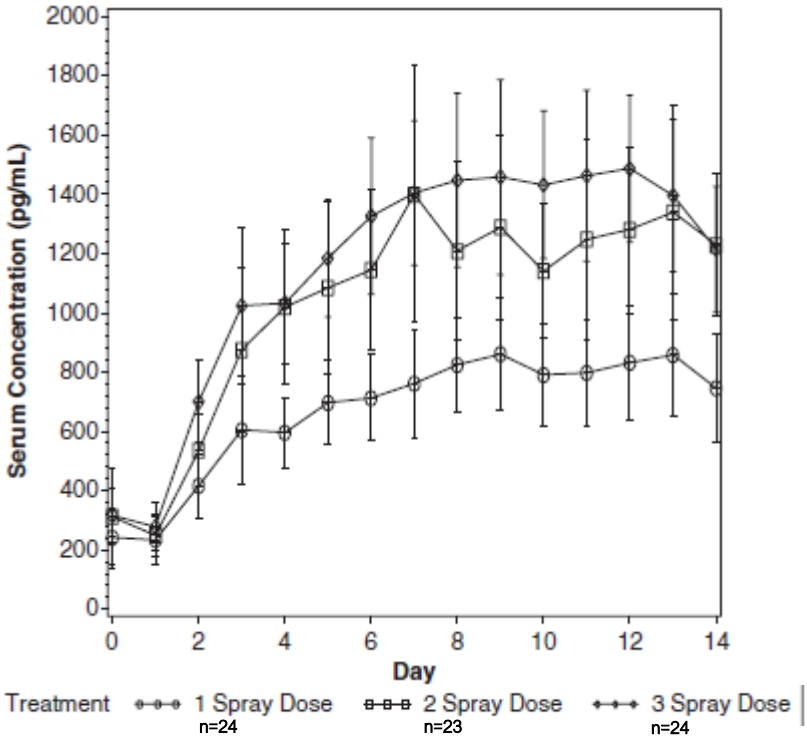
Mean serum estrone concentrations at baseline were between 14.9 and 17.1 pg/mL. Estrone concentrations with treatment were generally low, between 60–63 pg/mL at steady state (*Figure 2*).



Estrone sulfate pharmacokinetics

Figure 3: Mean (± standard error) predose estrone sulfate concentrations (Days 0–14)

Mean baseline estrone sulfate values ranged from 157–296 pg/mL and were low throughout the study period. The pattern of exposure and metabolism was similar to that of estradiol (Figure 3).



Other endpoints

In this study, 3 of 72 women using the transdermal estradiol spray reported ≥1 treatment-related adverse events. All treatment-related adverse events were mild-to-moderate in intensity and no serious adverse events or deaths were reported.

Effects of skin-to-skin contact, washing of the application site and use of sunscreen on estradiol absorption from a transdermal spray[27]

This study was undertaken to investigate the effects of skin-to-skin contact on the transfer of estradiol from a transdermal spray, and how washing the application site and the use of sunscreen at the site affected its pharmacokinetics.

Study summary

- Estradiol absorption was not affected when sunscreen was applied one hour before administration of the spray.
- Application of sunscreen one hour after administration of the spray resulted in a slight decrease in estradiol absorption.
- Washing the site of application 1 hour after administration had no significant effect on the systemic absorption of estradiol.
- The use of a transdermal estradiol spray did not result in a significant transfer of estradiol by skin-to-skin contact one hour after administration.

Study design and treatment

This was an open-label, single centre study in which 20 healthy female patients were treated with one dose of Lenzetto (three 90 µL sprays) once daily for 18 days. Three sprays of Lenzetto constituted one dose and each dose contained 4.59 mg estradiol. The application was left exposed to dry for 30 minutes before being covered by clothing.

The three sprays were applied on three non-overlapping sites on each woman's inner forearm. Twenty healthy males provided skin-to-skin contact for the study purposes but were not treated with the spray.

Study population

All patients were healthy postmenopausal women, aged 40–65 years, non-smokers, with BMI 19–30 kg/m^2 and serum estradiol less than 25 pg/mL. Men who participated were healthy, non-smokers, 35–63 years, had a BMI 20–30 kg/m^2, with serum estradiol below 25 pg/mL.
Men or women were excluded if they had skin allergies, contraindications to oestrogen therapy, any significant abnormal medical finding, history of any significant illness which could interfere with the test or make it dangerous, the possibility of drug abuse, or were on hepatic enzyme inducers.

Women were also excluded if they had a history of abnormal vaginal bleeding within the last 6 months or were on hormonal therapy for 1–8 weeks before the start of the study.

Study assessments and endpoints

The primary endpoint was the estradiol level in the serum of subjects following the application of the transdermal spray, skin-to-skin contact, washing of the site, or application of sunscreen. Other endpoints included adverse event monitoring.

Study results

Baseline demographics

A total of 20 healthy women were treated with the transdermal spray, and 20 healthy men participated in the skin-to-skin contact. Their baseline characteristics are described in Table 4.

Table 4: Overview of baseline characteristics (PK population)

Characteristic	Women (n=20)	Men (n=20)*
Mean age, years (SD)	54.2 (4.0)	51.6 (7.4)
Mean BMI, kg/m^2 (SD)	26.6 (2.7)	26.9 (2.8)
Race, n (%)		
White	0	1 (5.0)
Black	0	1 (5.0)
Hispanic/Latino	20 (100)	18 (90.0)

BMI=body mass index; PK=pharmacokinetics; SD=standard deviation
*The men were only included in the skin-to-skin transfer experiment.

Skin-to-skin transfer

The skin-to-skin transfer results are presented in Table 5. Significant transfer did not occur following skin-to-skin contact.

Table 5: Skin-to-skin contact assessment for Lenzetto (men's PK population)

PK parameter	Pre-contact (n=20)	Post-contact (n=20)	Ratio	90% CI
Untransformed values				
$AUC_{0\text{-}24}$, pg.h/mL (%)	550.9 (23.0)	572.2 (25.3)	-	-
C_{max}, pg/mL (%)	27.7 (21.1)	29.6 (26.2)	-	-
T_{max}, h	20 (0–24)	18 (16–20)	-	-
In-transformed values				
In $AUC_{(0\text{-}24)}$	538.0	556.5	1.03	1.00–1.07

$AUC_{(0\text{-}24)}$= area under the serum concentration-time curve from time 0 through 24 hours; C_{max}=maximum concentration; CI=confidence interval; PK, pharmacokinetic; T_{max}=median time to maximum concentration (minimum–maximum)

Washing effect evaluation

Washing the application site had no significant effect on estradiol exposure (Table 6).

Table 6: Washing effect assessment for Lenzetto (women's PK population)

PK parameter	Control estradiol (n=19)	Washed (n=19)	Ratio	90% CI
Unadjusted values				
$AUC_{0\text{-}24}$, pg.h/mL (%)	869.2 (71.08)	939.8 (82.4)	-	-
C_{max}, pg/mL (%)	62.7 (82.2)	61.0 (98.3)		
T_{max}, h	18.0 (0.0–24.0)	17.0 (0.0–22.0)		
In $AUC_{0\text{-}24}$	734.7	756.9	1.03	0.92–1.15
Baseline-adjusted values				
$AUC_{0\text{-}24}$, pg.h/mL (%)	721.4 (74.7)	793.8 (91.0)		
C_{max}, pg/mL (%)	52.5 (78.2)	54.6 (109.1)		
T_{max}, h	18.0 (0.0–24.0)	16.0 (0.0–22.0)		
In $AUC_{0\text{-}24}$	600.7	625.3	1.04	0.92–1.18

$AUC_{(0\text{-}24)}$=area under the serum concentration-time curve from time 0 through 24 hours; C_{max}=maximum concentration; CI=confidence interval; PK=pharmacokinetic; T_{max}=median time to maximum concentration (minimum–maximum)

Effect of sunscreen application

There was a slightly lower exposure to estradiol when sunscreen was applied 1 hour after the transdermal spray, as compared to sunscreen use 1 hour before the estradiol application (*Table 7*).

Table 7: Sunscreen effect assessment for Lenzetto (women's PK population)

PK parameter	Control estradiol (n=19)	Sunscreen 1 h before (n=19)	Sunscreen 1 h after (n=19)
Unadjusted values			
$AUC_{0-24,}$ pg.h/mL (%)	869.2 (71.1)	869.6 (59.8)	773.8 (62.5)
C_{max}, pg/mL (%)	62.7 (82.2)	56.3 (64.5)	55.3 (88.7)
T_{max}, h	18.0 (0.0–24.0)	18.0 (0.0–24.0)	21.0 (4.0–24.0)
Baseline-adjusted values			
$AUC_{0-24,}$ pg.h/mL (%)	721.4 (74.7)	710.8 (51.8)	656.2 (67.3)
C_{max}, pg/mL (%)	52.05 (78.2)	49.1 (66.1)	49.9 (98.0)
T_{max}, h	18.0 (0.0–24.0)	18.0 (0.0–24.0)	20.0 (4.0–24.0)

$AUC_{(0-24)}$=area under the serum concentration-time curve from time 0 through 24 hours; C_{max}=maximum concentration; CI=confidence interval; PK=pharmacokinetic; T_{max}=median time to maximum concentration (minimum–maximum)

Other efficacy and safety measures

Four women experienced one treatment-emergent adverse event: mild body aches (n=3) and mild lower back pain (n=1). There were no discontinuations due to treatment-emergent adverse events.

Safety and efficacy of a transdermal estradiol spray in women with postmenopausal vasomotor symptoms[3]

This Phase 3 study was conducted to investigate the safety and efficacy of a transdermal estradiol spray in 454 women with postmenopausal vasomotor symptoms.

Study summary

- This study demonstrates the efficacy and safety profile of the transdermal estradiol spray for the treatment of moderate-to severe vasomotor symptoms in healthy menopausal women.
- At Week 12, the majority (74–85%) of women on Lenzetto showed at least a 50% hot flush frequency reduction as compared with 46% in the placebo group.
- The dose regimen starts with one spray per day and can be increased to a maximum of three sprays per day to achieve higher estradiol levels.
- The three dose levels achieved efficacy at 0.021– 0.040 mg/day delivery rates and the spray was well-tolerated.

Study design and treatment

This was a Phase 3 randomised, double-blind, placebo-controlled, multicentre, parallel-group study in which 454 postmenopausal women were randomised to receive one, two, or three estradiol (90 µL spray containing 1.53 mg estradiol) or matching placebo sprays.
The area of application was on the ventral surface of the forearm, with adjacent but separate areas used if two or three sprays were used.

Study population

All subjects were naturally or surgically postmenopausal women, 35 years or older, with an average of at least eight moderate-to-severe hot flushes per day. All participants had to have had an adequate washout period from oestrogen-containing medications before starting the study. They also had to have a Pap test without dysplasia/malignancy, screening mammogram and breast examination without suspicion of malignancy, and, if the uterus was still present, endometrial biopsies free of hyperplasia or malignancy.

Women with known hypersensitivity to oestrogens or progestins were excluded from the study, as were women who used implants or injectables or pellets of these drugs within the last year or had a history of (or presence of) clinical conditions which made the use of these drugs dangerous. Women with skin contact allergy to medicated or other substances, active skin disease, or abnormal genital bleeding were also excluded.

Study assessments and endpoints

The primary efficacy endpoints were mean change from baseline in frequency and severity of moderate-to-severe hot flushes at Week 4 and 12.

Secondary efficacy evaluations included the mean weekly change in frequency and severity of moderate-to-severe vasomotor symptoms from baseline, the 50%, 75%, and 90% reduction of

frequency, change in Greene Climacteric scale score, and participant assessment of overall treatment effect. Safety assessments included adverse events (AEs) monitoring.

Study results

Baseline demographics

A total of 454 postmenopausal healthy women were randomised in the study, and overall demographics and baseline characteristics were well balanced between the study groups (Table 8).

Table 8: Overview of baseline characteristics (ITT population)

Characteristics	3 sprays		2 sprays		1 spray	
	Estradiol (n=76)	Placebo (n=75)	Estradiol (n=74)	Placebo (n=76)	Estradiol (n=76)	Placebo (n=77)
Age (years)	52.3 ± 5.7	52.0 ± 6.3	52.2 ± 6.8	52.0 ± 7.0	53.5 ± 6.8	52.8 ± 6.9
Race, n (%)						
White	49 (64.5)	49 (65.3)	53 (71.6)	58 (76.3)	54 (71.1)	55 (71.4)
African American	21 (27.6)	24 (32.0)	19 (25.7)	14 (18.4)	17 (22.4)	16 (20.8)
Asian	0	1 (1.3)	0	0	0	0
Hispanic	4 (5.3)	0	2 (2.7)	3 (3.9)	3 (3.9)	4 (5.2)
American Indian/ Alaskan native	1 (1.3)	0	0	0	0	0
Multiracial	0	1 (1.3)	0	1 (1.3)	2 (2.6)	1 (1.3)
Other	1 (1.3)	0	0	0	0	1 (1.3)
BMI (kg/m2)	27.3	26.8	27.0	27.5	27.0	26.4
Hot flushes	10.78	12.55	12.66	12.13	11.81	12.41
Menopausal status						
Surgical†	25	27	26	31	31	34
Natural‡	51	48	48	45	45	43

BMI=body mass index; ITT= Intent-to-treat
Data are mean (± standard deviation) or n (%) unless otherwise specified.
†Participants with a bilateral oophorectomy were considered surgically postmenopausal.
‡Naturally menopausal participants were considered to be any subject who had not undergone a bilateral oophorectomy.

Efficacy parameters

A statistically important reduction in the frequency and severity of vasomotor symptoms at Week 4 and Week 12 was observed with one, two and three sprays when compared with placebo, with the exception of the severity of symptoms following the application of one spray (Table 9).

Table 9: Effect of Lenzetto on the frequency and the severity of moderate to severe hot flushes at Week 4 and Week 12 (ITT population)

Endpoint	3 sprays		2 sprays		1 spray	
	Estradiol (n=76)	Placebo (n=75)	Estradiol (n=74)	Placebo (n=76)	Estradiol (n=76)	Placebo (n=77)
Frequency, mean change from baseline (SD)						
Week 4	-6.64 (4.23)	-4.54 (7.40)	-7.30 (6.93)	-4.74 (4.38)	-6.26 (4.01)	-3.64 (5.30)
P value	0.0002		0.0027		0.0010	
Week 12	-8.44 (4.50)	-5.32 (6.30)	-8.66 (6.65)	-6.19 (5.77)	-8.10 (4.02)	-4.76 (5.84)
P value	<0.0001		0.0099		0.0004	
Severity, mean change from baseline (SD)						
Week 4	-0.43 (0.66)	-0.13 (0.53)	-0.57 (0.83)	-0.25 (0.64)	-0.47 (0.80)	-0.19 (0.55)
P value	0.0031		0.0160		0.0573	
Week 12	-1.07 (1.01)	-0.31 (0.75)	-0.92 (1.01)	-0.54 (0.89)	-1.04 (1.01)	-0.26 (0.60)
P value	<0.0001		0.0406		<0.0001	

SD=standard deviation

Figure 4 shows the change in frequency of hot flushes over 12 weeks of transdermal spray application of estradiol for both treatment and placebo groups. The difference became statistically significant by week 2 of the study.

There was also a reduction in the severity of hot flushes in the treatment groups, which became significantly different from the placebo group at Week 3, 4, and 5, in the groups with three, two and one sprays of estradiol daily

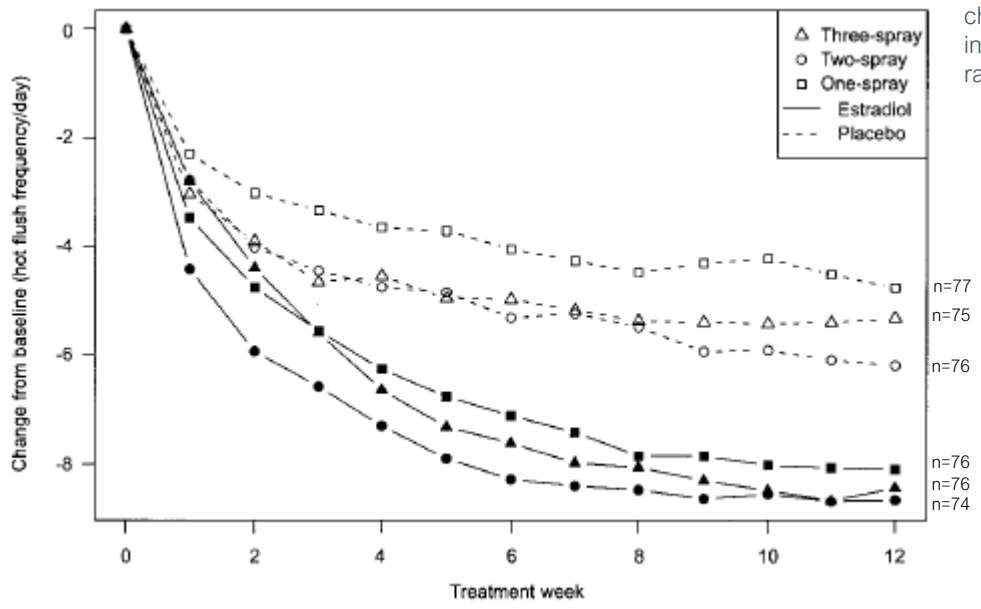
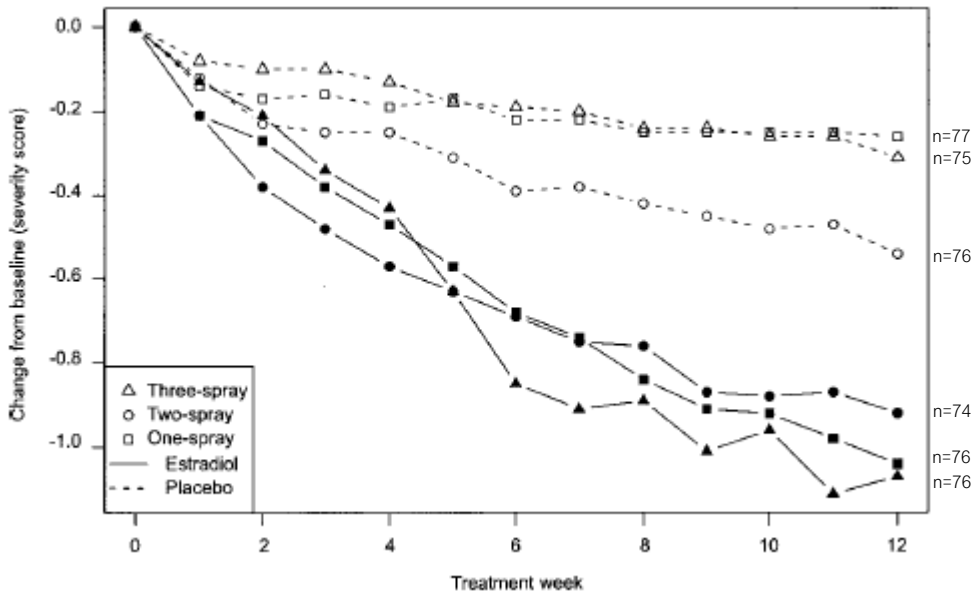


Figure 4: Weekly change from baseline in hot flush frequency rate over 12 weeks

Figure 5: Weekly change from baseline in hot flush severity scores over 12 weeks



Other endpoints

There was a significantly higher mean reduction in hot flush scores, night sweat scores, and in patient-reported global assessment scores across the treatment groups compared with the placebo groups.

Adverse events were reported in 129 (57.1%) women on estradiol and 114 (50.0%) women on placebo. Headache was the most frequently reported adverse event. There were no clinically significant differences observed in other parameters.

There were no severe treatment-emergent adverse events, and no deaths in either group.

Comparison of efficacy and local tolerability of estradiol metered-dose transdermal spray to estradiol patch in a network meta-analysis [28]

There are no direct head-to-head trials comparing Lenzetto with other HRT formulations. This network meta-analysis was carried out to compare the efficacy and local tolerability of a patch and a metered-dose transdermal spray that have never been directly compared.[28]

Study summary

Note: These are indirect data comparisons produced through meta-analysis

- The evidence suggests that effect of estradiol MDTS in reducing vasomotor symptoms is comparable to the estradiol patch of the similar dose. [27]
- The 100 and 50µg/d estradiol patch were the most effective treatments in reducing hot flushes. [27]
- The estradiol MDTS has a better application site reaction profile, in particular, the prevalence of skin irritation, itching and erythema, than the 14µg, 23µg, 25µg, 37.5µg, 45µg, 50µg, 75µg and 100µg estradiol patches. [28]
- Systemic adverse event profile of the estradiol MDTS seems to be slightly better than the average of estradiol patches. [27]

Endpoints

For the comparison of the efficacy of E2 MDTS with patches, the selected endpoint was the mean between-arm difference of the relative changes (%) in the number of hot flushes from baseline (week 0) to week 12. [28]

Study methodology

Literature search strategy

The aim of the systematic literature review was to identify: (1) placebo- or active-controlled clinical studies of E2 HRT with patches or MDTS that had efficacy endpoints of interest, or (2) other observational and patch versus placebo-controlled studies that had outcomes for local tolerability of patches.[28]

In addition, some efficacy and safety outcomes were used from the Clinical Study Report of the only phase-III, double-blind, multicenter, placebo-controlled clinical trial[3]

All searches were run in "Title" and "Abstract" fields (except in "Scopus" where "Key" field was involved also). Restricting to English language was the only limitation applied. Articles before 1995 were excluded.[29]

Four search engines were used covering the following databases (accessing dates in brackets)[29]:

- Scopus: Medline/Embase (accessed on 22nd October 2014)
- EBSCO: Academic Search Complete, CINAHL with Full Text, Health Source: Nursing/Academic Edition (accessed on 22nd October 2014
- OVID: EBM Reviews – Cochrane Methodology Register, EBM Reviews – Health Technology Assessment; EBM Reviews – NHS Economic Evaluation Database; Cochrane DSR, ACP Journal Club, and DARE; and International Pharmaceutical Abstracts (accessed on 20th October 2014)
- Cochrane: Cochrane Reviews (Reviews and Protocols), Other Reviews and Trials (accessed on 12th November 2014) (other Cochrane databases were searched via OVID)

Overall, eight randomized controlled studies could be included in the network meta-analysis.[28]

Network meta-analysis (NMA)

Network meta-analysis (NMA) is a suitable instrument when more than two treatment modalities need to be compared, and not only results of pairwise investigations are available. When decision making requires simultaneous comparison of several treatments that compete each other, NMA needs to be applied[30,31]. If results are available from both direct and indirect comparisons these can be integrated in an NMA in a coherent manner.[30,31] With this technique, it is also possible to assess the relative effects of two treatments which have never been compared to each other, but have been compared to shared other treatments. In this case the relative effects of the treatments of interest are estimated from the results of their direct comparisons to these other treatments. NMA also enables to calculate the probability that a specific treatment is the best (or the second or third etc. best), and allows the treatment ranking accordingly.[30,31]

For the NMA, nine treatments including placebo were generated from the treatment arms in the studies included. Figure 2 shows that all treatments but one (14 µg/day patch) resulted in a significantly greater relative reduction in the number of hot flushes than placebo.[28]

Study results

Hot flushes

In the efficacy analysis, eight active treatment arms and a placebo arm were determined based on the estradiol daily dose (from 14 µg to 50 µg). All but one had a significantly higher effect on relative change in the number of hot flushes than did the placebo (Fig. 2). We found no evidence for different efficacy of the patch and the metered-dose transdermal spray. The latter performed better in terms of local skin reactions.[28]

In a pairwise comparison of the treatments, a clear dose–response pattern could be shown: there was a small but statistically non-significant difference (6-7%) between the MDTS with 40 µg/day spray and the 50 µg/day matrix and 50 µg/day reservoir patches proved to be the most effective treatment.[28]

All of the pairwise comparisons showed similar results between MDTS versus patch treatment, in fact none showed significant differences.[28]

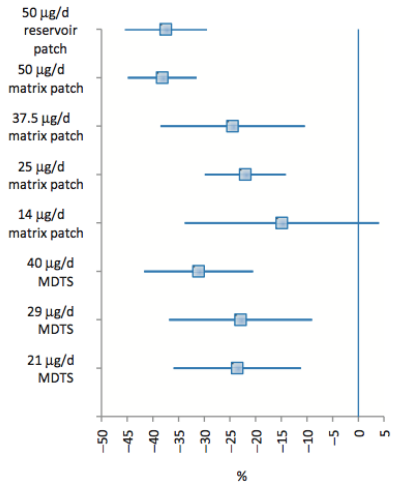


Figure 2. Mean difference in the relative change (%) of the number of hot flushes from week 0 to week 12 relative to placebo (error bars represent the 95% confidence intervals).

Local skin reactions

The ranges of the cumulative incidence of skin reactions across patch or MDTS during the study period varied from 1.3% to 54.9%. The figures for the placebo arms were roughly comparable to those for the active arms within each study. The E2 MDTS performed well compared to patches; the proportion of users with skin reactions was low, both on the active (1.3%) and on the placebo (1.8%) arms.[28]

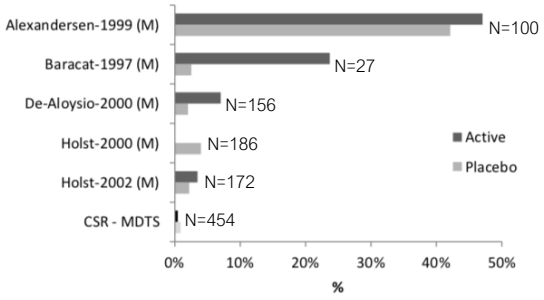
Compared to estradiol patches, the discontinuation rates due to local skin reaction were much lower with sprays. In the case of systemic adverse events, the discontinuation rate in the spray study was in the lower part of the range of the patch studies.[29]

The prevalence of skin irritation, itching and erythema was low with the estradiol spray and was better than the prevalence in patches, which was highly variable across different studies.[29]

Erythema

Five placebo-controlled trials and nine other observational were found that published data on the incidence of erythema. In cases of placebo-controlled trials, the variability of the results was large within a range of 0–47%.[28]

The E2 MDTS had an advantageous local tolerability profile in terms of erythema, since only a small number of patients experienced this sign: one case was reported in the 'one E2 spray' and two cases in the placebo arms (0.4% and 0.9%, respectively).[28]

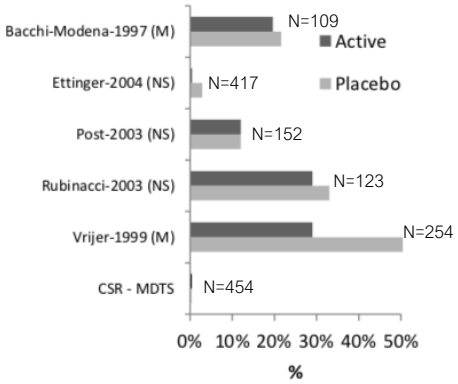


Cumulative incidence of erythema by treatment arm in the placebo controlled trials[28].
M= Matrix patch. **MDTS**= Metered-dose transdermal spray

Skin irritation

The variability of the results with patches in the five placebo-controlled trials ranged from 2.9% to 91.3%. In cases using the E2 spray, only one patient experienced skin irritation in the 'three E2 sprays arm' (1.3%).[28]

A small number of patch studies reported data on the incidence of itching with the results, varying from 0 to 66%. In cases of MDTS, one patient in the 'one E2 spray arm' and one in the 'two placebo sprays arm' experienced itching and one patient in the 'one E2 spray arm' experienced vesicles.[28]



Cumulative incidence of skin irritation by treatment arm in the placebo controlled trials.[28]
M= Matrix patch. MDTS= Metered-dose transdermal spray
NS= Not specified

Switching Guidelines

Two important factors should be taken into consideration when using HRT products: a) the lowest effective dose, and b) the shortest duration of usage.[1,32,33] Initiating Lenzetto therapy with the one-spray starting dose is recommended in every case regardless of the previously used HRT product, because a lower dose may be adequate to treat the patient's currently existing symptoms. Therefore, when switching from another HRT product, one spray of Lenzetto per day should be used initially. Taking a break between Lenzetto and other HRT products is not necessary. During the switching period, it is possible that some symptoms may reappear, but they may cease after the steady-state concentration is reached. After 4 weeks of continuous treatment with Lenzetto, a dose increase should be discussed if symptoms do not disappear.[34] The maximum daily dose is 3 metered-dose sprays (4.59 mg/day).[1]

Adverse Events

Tabulated list of adverse reactions[1]

Adverse events reported at a frequency of <10% are presented in Table 1, based on a 12-week, randomised, placebo-controlled trial in 454 women.[1]

Table 1: Adverse events reported[1]

System Organ Class (MedDRA 12.0)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Immune system disorders		Hypersensitivity reaction	
Psychiatric disorders		Depressed mood, Insomnia	Anxiety, Libido decreased, Libido increased
Nervous system disorders	Headache	Dizziness	Migraine
Eye disorder		Visual disturbances	Contact lens intolerance
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Palpitations	
Vascular disorders		Hypertension	
Gastrointestinal disorders	Abdominal pain, Nausea	Diarrhoea, Dyspepsia	Bloating, Vomiting
Skin and subcutaneous tissue disorders	Rash, Pruritus	Erythema nodosum, Urticaria, Skin irritation	Hirsutism, Acne
Musculoskeletal and connective tissue disorders		Myalgia	Muscle spasms
Reproductive system and breast disorders	Breast pain, Breast tenderness, Uterine/Vaginal bleeding including spotting, Metrorrhagia	Breast discolouration, Breast discharge, Cervical polyp, Endometrial hyperplasia, Ovarian cyst, Vaginitis	Dysmenorrhoea, Premenstrual-like syndrome, Breast enlargement
General disorders and administration site condition		Oedema, Axillary pain	Fatigue
Investigations	Weight increased, Weight decreased	Gamma-glutamyltransferase increased, Blood cholesterol increased	

From post marketing surveillance, skin and subcutaneous tissue disorders have been reported, including alopecia, chloasma, and skin discolouration.[1]

Description of selected adverse reactions

Breast cancer[1]

- 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[1]
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestogen combinations[1]
- The level of risk is dependent on the duration of use[1]
- Results of the largest randomised placebo-controlled trial (WHI study) and largest epidemiological study (MWS) are presented in Table 2 and Table 3.

Table 2: US WHI study – Additional risk of breast cancer after 5 years' use[1]

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 & progestogen‡			
50–79	14	1.2 (1.0–1.5)	+4 (0–9)

CEE=conjugated equine oestrogens; CI=confidence interval; HRT=hormone replacement therapy; MPA=medroxyprogesterone acetate
*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.

Table 3: MWS – Estimated additional risk of breast cancer after 5 years' use[1]

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period*	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)

CI=confidence interval; HRT=hormone replacement therapy
*Taken from baseline incidence rates in developed countries.
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration of 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.

Endometrial cancer[1]

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.[1]

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer.[1]

Depending on the duration of oestrogen-only use and oestrogen dose, the increased 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 MWS, 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]).[1]

Ovarian cancer[1]

Use of oestrogen-only and combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed.[1]

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 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 will be diagnosed with ovarian cancer over a 5-year period.[1]

Venous thromboembolism[1]

HRT is associated with a 1.3–3-fold increased relative risk of VTE. The occurrence of VTE is more likely in the first year of using HT. Results of the WHI studies are presented in Table 4[1]

Table 4: WHI Studies – Additional risk of VTE over 5 years' use[1]

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)
Oral oestrogen-only*			
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)

CI=confidence interval; HRT=hormone replacement therapy
*Study in women with no uterus

Coronary artery disease[1]

The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestogen HRT over the age of 60.[1]

Ischaemic stroke[1]

The use of oestrogen-only and oestrogen plus 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. Data on ischaemic stroke risk in the WHI studies are presented in Table 5.[1]

Table 5: WHI studies combined – Additional risk of ischaemic stroke* over 5 years' use[1]

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)
50–59	8	1.3 (1.1–1.6)	3 (1–5)

CI=confidence interval; HRT=hormone replacement therapy
*No differentiation was made between ischaemic and haemorrhagic stroke.

Additional reported adverse reactions[1]

The following additional adverse reactions have also been reported with oestrogen and/or progestin therapy: angioedema, anaphylactoid/anaphylactic reactions, glucose intolerance, mental depression, mood disturbances, irritability, exacerbation of chorea, exacerbation of epilepsy, dementia exacerbation of asthma, cholestatic jaundice, increased incidence of gallbladder disease, pancreatitis, enlargement of hepatic haemangiomas, chloasma or melasma, that may persist when drug is discontinued; erythema multiforme, haemorrhagic eruption, loss of scalp hair, arthralgias, galactorrhoea, fibrocystic breast changes, increase in size of uterine leiomyomata, change in amount of cervical secretion, changes in cervical ectropion, vaginal candidiasis, hypocalcaemia (pre-existing condition).[1]

Reporting of suspected adverse reactions[1]

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ Adverse events should also be reported to Gedeon Richter (UK) Ltd on +44 (0) 207 604 8806 or drugsafety.uk@gedeonrichter.eu

Overdose[1]

Effects have not been reported following acute ingestion of large doses of oestrogen-containing products. Overdosage of oestrogen may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of Lenzetto together with institution of appropriate symptomatic care.[1]

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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

Further information is available from: Gedeon Richter UK Ltd, 127 Shirland Road, London W9 2EP. Tel: +44 (0) 207 604 8806. Email: medinfo.uk@gedeonrichter.eu

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Date of preparation of PI: February 2020

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ 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

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